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FOREWORD

It gives me great pleasure to write a foreword for this issue of *The American Surgeon* wherein will be given some characteristic illustrations of the work of the members of our Department of Surgery at the University of California, Los Angeles. Inspection of previous numbers of *The American Surgeon* provides proof of the very high quality of surgical research in other institutions—so much so that a Dean's natural modesty is easily strained in rising to defend the high quality of his own confreres. One need only to admit to high quality in the competition in order to establish high quality in one's own competing team. Having established the high level of this competition, I can now let the papers speak for themselves.

Historically, the Department of Surgery of the University of California at Los Angeles School of Medicine was activated in 1948. The first class, consisting of 28 students, was admitted to the temporary quarters of the U. C. L. A. Medical School in the fall of 1950, and the present permanent quarters of the School for the Department of Surgery were occupied during the summer months of 1955. Throughout these years staff members of this institution, working in a variety of facilities, have consistently made significant clinical and laboratory investigative contributions. Much work is still going on in temporary quarters and wooden shacks.

The 11-year period since this Department of Surgery was activated has been an exciting period in the development of all fields of medical science. Certain of the advances in the surgical fields have been particularly spectacular.

Great strides have been made throughout the world in the field of cardiac surgery; first, with closed cardiac operations and in recent years in the field of open cardiac surgery. Operations for aneurysm and obstruction of the aorta and large arteries have been developed and their place in the surgeon's armamentarium established. Further information has been added to our basic knowledge of fluid and electrolyte behavior, adrenal cortical steroid activity, wound infections, the use of hypothermia and, although the clinical solution to the problems of malignant cell growth and homograft survival have not as yet been forthcoming, significant advances in these all important fields have been made. We are pleased that various members of our faculty in many different disciplines have added their bit to the advance of these various fields of such importance to the surgeon.

The papers presented in this issue illustrate the wide range of investigative effort of a modern surgical department, both in the advance of new ideas and the further study and refinement of older concepts. Such critical study, experimentation, evaluation and presentation keep all aspects of medical science prepared to meet the changing aspects of disease problems and constantly alert to methods of improving our management of illness and disability.

One can say that for a young Department of Surgery an image of scholarly achievement has been established in a clinical environment. Although much of this in the end stems from the men themselves, the primary support of the environment which makes this possible comes from the general campus policies and attitudes, of which the School of Medicine has become so much an integral part. In part, the change comes about in the area of graduate education and research. The struggle which medical schools are having to legitimatize faculty time for research can be clearly defined in University policy for other faculties. Support comes from the campus

when the question is raised: Why not treat the Medical Faculty like the rest of the University Faculty insofar as policy on research facilities and time are concerned? From the union of a medical school with a university campus there comes the stabilizing forces which we believe will enable our departments to continue their research productivity throughout the future years.

STAFFORD L. WARREN, M.D., *Dean*

TRANSPLANTATION OF THE PAROTID DUCT FOR XEROPHTHALMIA*

FRANKLIN L. ASHLEY, M.D., AMOS N. SCHWARTZ, D.D.S., M.D.,
BRADLEY R. STRAATSMA, M.D., AND JAMES C. FORD, M.D.

Los Angeles, California

Many methods for the conservative management of total xerophthalmia have been described in the contemporary literature. These include topical instillation of artificial tears, administration of vitamin A, and the surgical procedures of oral mucous membrane transplantation, tarsorraphy and occlusion of the lacrimal puncta.[3,4] None of these methods offers a complete solution to this difficult problem.

A surgical approach which affords a greater measure of permanent improvement has recently been introduced. This technique converts parotid gland secretions to an ocular lubricant by transplantation of the parotid duct to the inferior conjunctiva cul-de-sac. The method provides a readily available and continual source of lubrication and eliminates the inconvenience of artificial tear instillation.

The first report of this procedure in the American literature was by Bennett and Bailey,[2] in 1957. This article describes a case from the Opthalmology Section, Department of Surgery, Crile Veterans Administration Hospital, Cleveland, Ohio, and includes a review of the Russian and Chinese literature on the subject. The Russian and Chinese authors state that no serious complications were observed and, in each case, there was an improvement in visual acuity.

Total xerophthalmia often follows trachoma, exfoliative dermatitis, and ocular pemphigus. The destruction of the lacrimal gland and accessory lacrimal tissue eventually leads to total blindness.

Three cases are presented in this series; 2 patients gave a history of ocular pemphigus and the 3rd a history of Stevens-Johnson disease.

ANATOMY

The general course of the parotid gland duct (Stensen's duct) follows that of a straight line extending from the lobule of the ear to a point midway between the nasal ala and the vermilion of the upper lip. It originates from the union of a number of ductal tributaries at the midportion of the anterior border of the gland and projects forward on the lateral side of the masseter muscle, approximately one-half inch below the border of the zygomatic arch. The duct then turns abruptly and passes medialward around the anterior border of the masseter muscle to pierce the buccal fat, buccinator muscle, and mucous membrane.[5,6] In the oral cavity, its orifice can be identified in the buccal vestibule opposite the crown of the upper second molar. In its passage lateral to the masseter muscle, it is accompanied by a zygomatic branch of the facial nerve below and by the transverse facial artery above (fig. 1*A*). In general, these structures have a course parallel to the duct. In its passage across the masseter muscle, it receives an accessory or tributory duct from the accessory parotid gland. The wall of the main duct consists of fibrous tissue intermixed with smooth muscle fibers and appears as a glistening white, thick, tough structure, approximately 3 mm. in diameter.

SURGICAL TECHNIQUE

Under general endotracheal anesthesia, an infraorbital block and infiltration of the operative site is performed using 1 per cent Xylocaine containing 1:100,000 Adrenalin to produce local ischemia and ballooning of the periductal connective tissue. A no. 3 ureteral catheter is inserted into the duct papilla and threaded up to the parotid gland with moderate pressure so as to produce an outward bowing of the duct beneath the skin of the cheek readily palpable by the operator. A vertical incision, slightly curved to conform to the skin lines and approximately 2 cm. in length, is made over the anterior border of the masseter muscle. It is placed in such a way that the incision line is bisected by a line from the lobule of the ear to a point midway between the nasal ala and the upper lip vermilion (fig. 1*B*). When the subcutaneous tissues are exposed, the

* From the Department of Surgery, Divisions of Plastic Surgery and Ophthalmology, University of California Medical Center, Los Angeles, California.

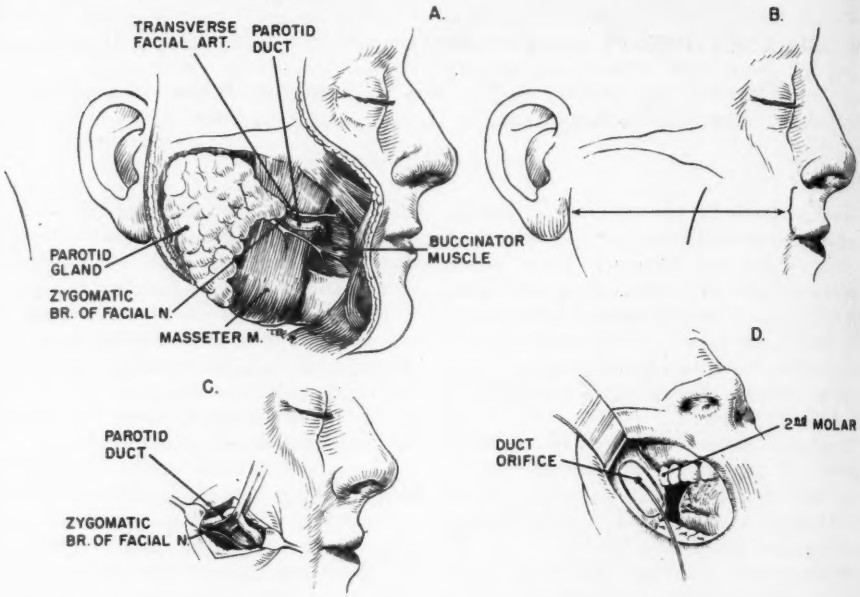

FIG. 1. Artist's drawings illustrating: *A*, anatomy of the parotid duct; *B*, imaginary line along the course of the duct bisecting the skin incision; *C*, exposure of the parotid duct with preservation of the parallel branch of facial nerve; *D*, incised mucous membrane cuff with no. 3 ureteral catheter in position.

duct is then identified and isolated by blunt dissection in a line parallel to its course to assure preservation of the facial nerve branches (fig. 1*C*). The duct is completely mobilized proximally to the gland substance, being careful to preserve its junction with the accessory duct, and distally to the mucous membrane surrounding the duct papilla. At this stage, through the oral approach, a cuff of mucous membrane 2 by 3 cm. in dimension is incised with the duct papilla at its center vertically, but at the juncture of the posterior and middle third horizontally (fig. 1*D*). The dissection is completed to allow complete mobilization of the duct and its attached mucous membrane cuff. All fat and excess connective tissue is trimmed from the mucous membrane of the cuff and the duct is extended by forming a tube from the cuff of mucous membrane. The oral wound is closed with interrupted 6-0 nylon sutures and a small Penrose drain inserted.

Through the skin incision on the cheek, blunt dissection is used to develop a subcutaneous tunnel from the origin of the parotid duct to the inferior conjunctival cul-de-sac at the junction of its lateral and middle thirds (fig. 2*A*). Through this tunnel, the duct with its attached cuff is drawn, without rotation or kinking, to be attached to the conjunctiva of the inferior fornix. The mucous membrane cuff, when tubed in its new position, forms a funnel increasing the length of the transplanted duct and allowing its placement without undue tension. This increase in duct length is essential for the prevention of ectropion, entropion, or duct stricture. The cuff margins are sutured to the conjunctiva with interrupted 5-0 plain catgut and 6-0 nylon sutures (fig. 2*B*). The subcutaneous tissues are closed with interrupted 4-0 plain catgut sutures and the skin with interrupted 6-0 nylon sutures (fig. 2*C*). Ophthalmic Neosporin is placed in the conjunctival sac and the eyes are covered with eye pads and a pressure dressing. These dressings and the oral wound drain are removed on the 2nd postoperative day.

This technique has been applied successfully to both eyes in the 1st patient of the series, and to one eye of each of the remaining patients.

CASE REPORTS

Case 1. On October 16, 1957, C. C., a 75-year-old white man, was admitted to the University of

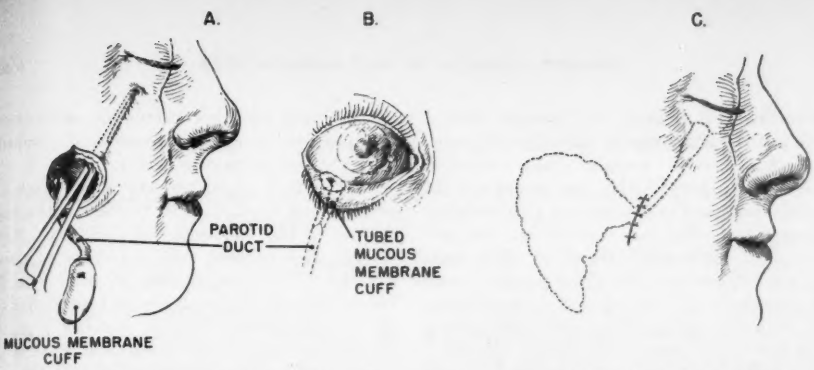

FIG. 2. Artist's drawings illustrating: *A*, forceps in subcutaneous tunnel to inferior cul-de-sac; *B*, tubed mucous membrane cuff sutured to conjunctival cul-de-sac; *C*, transplanted position of parotid duct at completion of procedure.

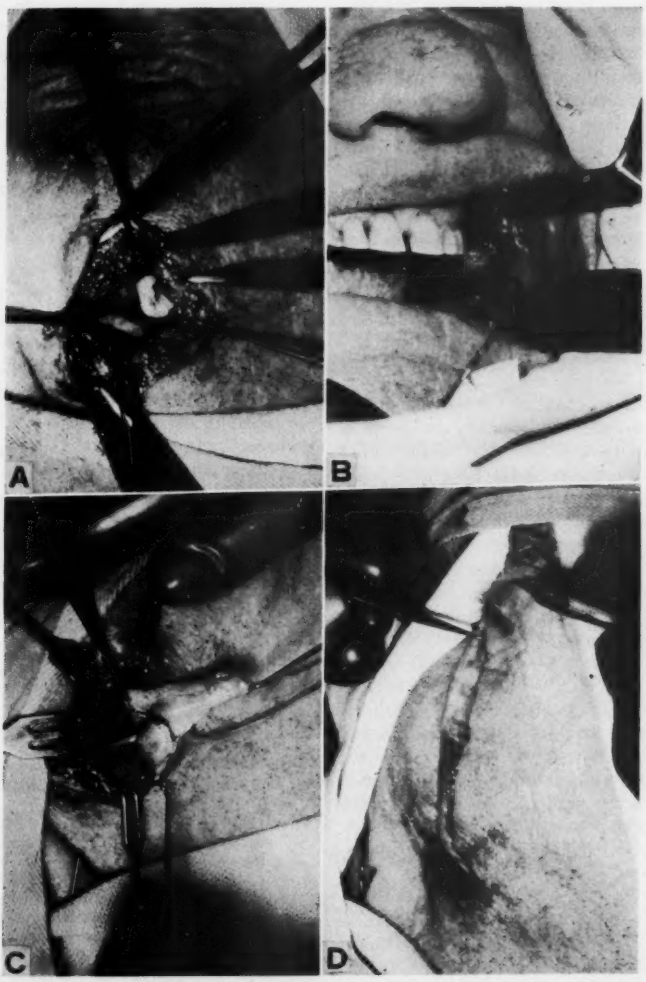

FIG. 3. Photographs of patient illustrating principles diagramed in figures 1 and 2: *A*, exposed parotid duct in site; *B*, oral view of incised mucous membrane cuff; *C*, mucous membrane cuff withdrawn through face wound (catheter sutured in orifice); *D*, completely mobilized duct with attached mucous membrane cuff in position to demonstrate adequate length.

California Medical Center, Los Angeles, with a 4-month history of decreasing vision in both eyes. Physical examination revealed that corrected distance visual acuity in the right eye was light perception only, and in the left eye was counting fingers at 8 feet. The conjunctival sac was dry and virtually obliterated bilaterally. The right cornea was opaque and the globe interior could not be visualized; the lower half of the left cornea showed scarring, although the iris could be seen and the left pupil reacted briskly to accommodation and direct and consensual light. The diagnosis was bilateral ocular pemphigus with symblepharon.

On January 10, 1958, under local anesthesia, the symblepharon of the lower fornix of the left eye was severed and the new sulcus lined with a mucous membrane graft from the lower lip. On March 3, 1958, a similar procedure was performed on the left upper fornix. The xerosis did not improve following these two procedures and on August 18, 1958, a parotid duct transplant was performed successfully. The cornea cleared markedly and visual acuity increased. The copious epiphora following this operation made it necessary to re-establish the nasolacrimal duct destroyed by the original disease process. This was performed on February 9, 1958, using the technique described earlier by the senior author.[1] The reconstructed nasolacrimal apparatus has continued to function well to this date with marked relief of tearing. A concomitant mucous membrane graft was attached to the right lower fornix with release of symblepharon. On April 9, 1959, the symblephara of the right upper fornix were released, a mucous membrane graft placed in the fornix, and a successful parotid duct transplant to this eye performed.

Visual acuity has increased in both eyes and, after further observation, a corneal transplant to the left eye is contemplated.

Case 2. R. D., a 27-year-old white man, was admitted to the Wadsworth General Hospital, Veterans Administration Center, Los Angeles, on December 8, 1958, with a history of Stevens-Johnson disease in 1950, culminating in xerosis of both eyes. Physical examination revealed grossly normal extraocular structures except for bilateral entropion. There was bilateral corneal scarring, more marked on the right. Visual acuity in the right eye was light perception and in the left eye, finger counting at 6 inches with marked photophobia.

On December 9, 1958, a left parotid duct transplant was performed successfully with increase in visual acuity to finger counting at 24 inches and decreased photophobia. On March 31, 1959, a nasolacrimal duct reconstruction was achieved for epiphora. A similar procedure is planned for the right eye in the near future.

Case 3. T. R., a 56-year-old white woman, was admitted on April 12, 1959, to the Ophthalmology Service of the University of California Medical Center, Los Angeles, with a history of essential atrophy of the conjunctiva of both eyes for 7 years. During a 4½-year period before admission, operations included mucous membrane grafts to the left eye on two occasions, and mucous membrane grafts with canthoplasties to the right eye on three occasions. In addition, two attempts at corneal grafting to the left eye resulted in opacity and failure.

Physical examination on admission revealed bilateral xerophthalmia. The left eye was aphakic and the corneal transplant was clouded.

On April 13, 1959, a right parotid duct transplant was performed. The postoperative course was uneventful, with discharge from the hospital on the 6th postoperative day. The convalescence has been satisfactory to this date, with adequate tearing or salivation from the transposed duct, and the cornea is less opaque.

SUMMARY

A modified technique of parotid duct transplantation for xerophthalmia has been applied successfully to three patients whose eyes were afflicted with atrophy of the lacrimal gland, loss of the accessory lacrimal glands, and essential shrinkage of the conjunctiva. This technique, as described in the text, offers one permanent, direct, and easily executed solution to the difficult problem of the management of xerophthalmia.

Dr. Franklin L. Ashley
University of California Medical Center
Los Angeles 24, California

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CARCINOMA OF THE EXTRAHEPATIC BILE DUCTS*

HARVEY N. LIPPMAN, M.D., LLOYD C. MCDONALD, M.D., AND WILLIAM P. LONGMIRE, JR., M.D.

Los Angeles, California

Malignancy of the extrahepatic biliary ducts often presents a most difficult technical problem in surgical management. By their very nature many of these cases are "incurable" from the time they are first seen by the surgeon, and because of their tendency to be slow-growing tumors, palliation often becomes the most important consideration. The relief of intractable pruritis may alone warrant an operative procedure designed to decompress the biliary tract.

The level of the tumor in the extrahepatic biliary tree is the single most significant factor in determining the operability of this disease as well as the degree of palliation that one may anticipate. In the same manner, the level of the lesion determines the type of operative procedure which may be employed.

The surgical literature in general invokes a pessimistic attitude in regard to the operative management of patients with carcinoma of the extrahepatic biliary ducts. In the authors' experience, however, such a position is not justified. It is our feeling that an aggressive surgical approach should be utilized whenever possible. This may be done with a low operative mortality and often very gratifying results. Summarized briefly herein are pertinent clinical and pathologic data which have been helpful. Various surgical procedures are discussed and our own experience reviewed.

INCIDENCE

Primary carcinoma of the extrahepatic biliary tree is a relatively rare disease. In a series of 13,330 autopsies performed at the Cook County Hospital and reviewed by Kirshbaum and Kozoll,[11] there were 62 cases of carcinoma of the extrahepatic bile ducts which constituted an incidence of 0.46 per cent of the postmortem examinations and 3.4 per cent of all carcinomas in their series. Of these 62 autopsied cases, 76.7 per cent had metastatic lesions.

* From the Department of Surgery, University of California Medical Center, Los Angeles 24, California.

The incidence of malignancy in different areas of the extrahepatic biliary ducts varies markedly. The most common site of primary tumor appears to be the junction of the right and left hepatic ducts with the common hepatic duct. Next, in decreasing order of frequency, are the common bile duct, ampullary region, right or left hepatic ducts and the cystic duct.[1] Ampullary lesions account for 10 to 15 per cent of primary malignant neoplasms of this region. Because of their location, they often cause symptoms earlier than the others and thus afford a better chance for cure by surgical management.

PATHOLOGY

The low grade of malignancy of these tumors has been previously emphasized,[2, 5, 8, 9, 17] although some authors have taken exception to this.[16]

There are three basic types of carcinoma of the bile ducts: (1) medullary, (2) infiltrating and (3) papillary. There is no apparent predilection of any type of lesion for a particular segment of the bile duct system. Medullary lesions are usually more rapidly growing and metastasize widely and relatively early. Medullary carcinomas here as elsewhere in the body are highly cellular tumors. Infiltrative carcinomas are particularly apt to be slow growing. They are associated with abundant fibrous tissue reaction and may be difficult to differentiate from a benign stricture at the time of operation. The spread of infiltrating lesions is usually by direct extension. Biliary tract obstruction may be a late development. The papillary form of biliary tract carcinoma is rare. It is usually slow growing and late to metastasize, although it may precipitate early jaundice when strategically located.

The distinction between one type of tumor and another may be of prognostic significance. Of particular importance in this regard is the differentiation between a primary carcinoma of the intrapancreatic portion of the common bile duct and a carcinoma of the head of the pancreas. We have adopted certain criteria which are helpful

in making this distinction and which should be credited to Dr. Hugh Edmondson, Professor of Pathology, University of Southern California.[7] In lesions of the bile duct the tumor can be seen grossly to center about the duct compressing it from all sides, whereas in lesions of the pancreas the duct is compressed eccentrically from the outside. In duct carcinoma there may be actual ulceration and necrosis of the mucosa, whereas pancreatic tumors may invade the duct for some distance in the submucosal layer without involving the mucosa. The cells of a ductal lesion are often well differentiated with a basally placed nucleus and a large amount of clear cytoplasm.

Carcinoma of the ampulla of Vater may arise from the mucosa of the common bile duct or the duodenum. The junction between these two types of epithelium, however, is usually the source. Lesions of the ampulla are characteristically papillary tumors of low growth potential. D'Offay[6] reviewed 182 cases of ampullary carcinoma and demonstrated an incidence of metastasis in only 24 per cent of the patients.

CLINICAL FINDINGS AND DIAGNOSIS

In the 20 cases included in this review of our own experience there were 12 men and 8 women patients. This is in keeping with the experience of others who have reported a higher incidence of this disease in men. The ages of the patients ranged from 34 to 91 years with an average age of 60.3 years.

Jaundice, weight loss and pain constitute the usual trilogy of symptoms seen in this disease. Other symptoms may include anorexia, fever, diarrhea or constipation and vomiting. The nature of the pain is often variable and inconstant. It is usually located in the midepigastric area or in the right upper quadrant of the abdomen. It may be dull and aching or cramping in character, and often follows a meal.

Carcinoma in a bile duct may precipitate acute cholecystitis[18] or simulate chronic cholecystitis or peptic ulcer. Pain is explained by distention of the biliary passages or invasion of the numerous peribiliary nerve filaments.

Weight loss is usually the result of prolonged anorexia and inadequate assimilation of food. Obstructive jaundice, if unrelieved, eventually leads to biliary cirrhosis, portal hypertension and hepatic failure and these in turn may lead to the death of the patient before the tumor has advanced beyond the stage of operability.

The definitive diagnosis of extrahepatic biliary duct carcinoma may be difficult. Jaundice is usually the presenting complaint and may be the only physical finding. In the presence of jaundice, roentgenography is usually of little value. Attempts to visualize the extrahepatic biliary ducts in a patient with a serum bilirubin above 2 mg. per cent are usually fruitless although occasionally in the exceptional case one will gain considerable information from an intravenous or even an oral cholecystogram. Hodes and associates[10] state that it is difficult or impossible to differentiate ampullary lesions preoperatively by radiologic techniques and that the diagnosis must be established by history and physical findings. These authors state further that ampullary lesions do not cause widening of the duodenal loop, but add that there may be recognizable changes in duodenal mobility. Often a duodenal "impression" is seen in the postbulbar segment secondary to a dilated common duct.

The differential diagnosis of bile duct cancer includes any disease which causes jaundice. In the last analysis the important consideration lies in the differentiation of so-called nonsurgical from surgical jaundice. Once this distinction is made the exact diagnosis is largely academic, since the treatment is the same. If the patient is explored, operative cholangiography may be of considerable value.

TREATMENT

The surgical management of these lesions is governed largely by the location of the tumor. Those tumors occurring high in the hepatic ducts at the hilus of the liver can rarely be removed and even palliation is difficult to accomplish. Resection of the left lobe of the liver with intrahepatic cholangiojejunostomy has been employed with satisfaction in a few instances,[20] although this operation was designed originally for intractable benign biliary stricture.[12-15] It is occasionally possible to accomplish satisfactory biliary decompression by the introduction of a cannula or the limb of a T-tube through the tumor into the proximal ducts. Such patients may do exceptionally well. We have had one such gratifying experience (see case 1) and others are reported.[9]

As one considers lesions somewhat lower down

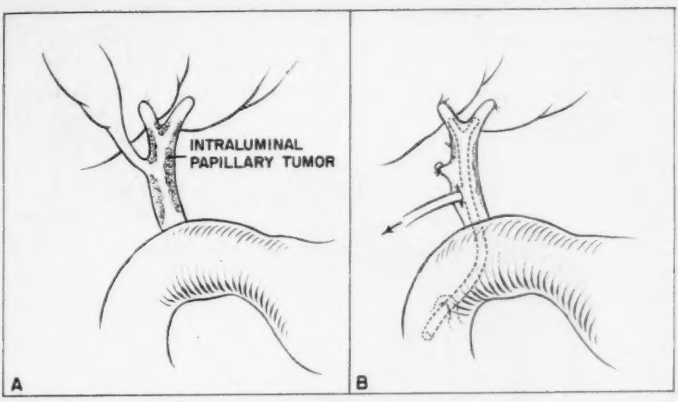

FIG. 1. Carcinoma of the extrahepatic bile ducts: intraluminal tumor reamed out with curette and T-tube to be left in place indefinitely (refer to case 1).

in the biliary tree, several possible procedures are suggested. On those rare occasions when it might be feasible, a simple local excision and end-to-end anastomosis could be utilized although this would not be the procedure of choice. When a local resection is all that can be considered, we should prefer to bring up a defunctionalized Roux-Y limb of jejunum for anastomosis to the proximal biliary duct. If the lesion can be completely circumscribed and the patient can tolerate the procedure, one should consider seriously employing a "curative" procedure such as the radical pancreaticoduodenectomy. At the present writing there is no doubt of the value of this operation for lesions of the ampulla of the common bile duct or for carcinoma of the papilla of Vater, although there has been considerable loss of enthusiasm in the use of this procedure for carcinoma of the head of the pancreas where it has been shown to be of relatively little value in terms of 5-year survival. The mortality rate for this operation approaches 30 per cent in some reported series[4], although this has not been our experience.

The remaining surgical alternative is a short-circuiting procedure of some type. A Roux-Y choledochojejunostomy or hepaticojejunostomy is preferred whenever possible, although cholecystojejunostomy or cholecystoduodenostomy may be preferable when the tumor is particularly bulky and the prognosis especially poor.

CASE REPORTS

The following case reports are representative of some of the methods of surgical management which we have employed for the control of carcinoma of the extrahepatic bile ducts. The accompanying schematic drawings serve to demonstrate the location of the tumor, the structures resected and the methods employed in re-establishing intestinal and biliary continuity.

Case 1 (see fig. 1). This patient was a 69-year-old Caucasian woman who entered U.C.L.A. Medical Center for the first time on August 22, 1957, complaining of "yellow skin" and itching of 14 days' duration. One month before admission she noted increasing fatigability; 2 weeks later her skin became yellowish in color followed shortly thereafter by the appearance of "pure white" stools. She had lost 10 pounds in weight in the preceding 30 days. Her laboratory data suggested an obstructive type of jaundice and an upper gastrointestinal series revealed only a small diverticulum in the second portion of the duodenum. On September 4, 1957, the patient was explored with a preoperative diagnosis of carcinoma of the head of the pancreas. The pancreas was normal but on palpation of the right and left hepatic bile ducts freely moveable tissue masses were noted within the two lumina. The common duct, which was of normal caliber, was opened and immediately friable, purplish red tumor tissue was extruded. Several cubic centimeters of this tissue were removed by means of a small curette and saline irrigations. An operative cholangiogram revealed

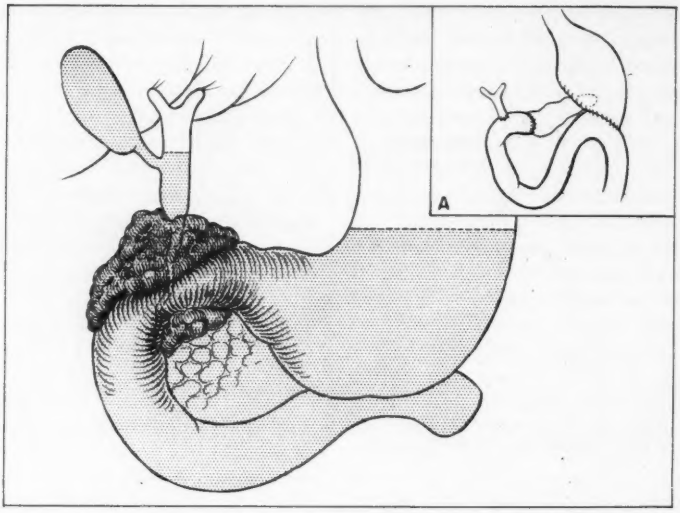

FIG. 2. Carcinoma of the extrahepatic bile ducts: resectable lesion involving distal end of the common bile duct and adjacent pancreas and duodenum. Radical pancreaticoduodenal resection with re-establishment of biliary and intestinal continuity as in *A* (refer to case 2).

a filling defect in the common hepatic duct and the left hepatic duct did not visualize. The choledochotomy was extended into the common hepatic and left hepatic ducts and more of the same type of tumor tissue was removed until there was a free flow of bile from the left and the right hepatic ducts. The distal common duct and papilla of Vater were uninvolved by tumor. The common duct was carefully closed around a T-tube which was brought through a stab wound in the abdominal wall. The patient tolerated the procedure quite well. Her jaundice cleared promptly and her stools regained their normal color. She was discharged with the T-tube *in situ* on her 17th postoperative day. She has been followed regularly in the outpatient department and was last seen 21 months after her operation at which time she continued to maintain her usual weight. The T-tube drains well with weekly irrigations by the patient. Her appetite is good and she is not jaundiced.

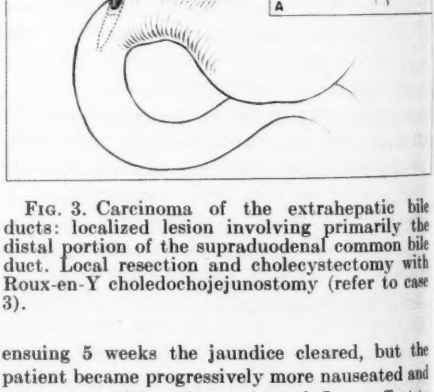

FIG. 3. Carcinoma of the extrahepatic bile ducts: localized lesion involving primarily the distal portion of the supraduodenal common bile duct. Local resection and cholecystectomy with Roux-en-Y choledochojejunostomy (refer to case 3).

Case 2 (see fig. 2). This patient was a 58-year-old Caucasian man who had been entirely well until 3 months before admission, when he noted onset of fatigability and anorexia. This was followed by "bloating" and "heartburn" after meals. He subsequently became jaundiced and was admitted to another hospital for surgery. At that time he was explored and found to have a large tumor mass in the head of the pancreas which was partially obstructing the duodenum. A cholecystogastrostomy was performed. During the ensuing 5 weeks the jaundice cleared, but the patient became progressively more nauseated and soon was vomiting after each meal. In an effort to relieve a suspected duodenal obstruction, he was re-explored at the U.C.L.A. Medical Center on March 5, 1957. When the resectability of the lesion was determined, a radical pancreaticoduodenectomy was performed. The patient recovered from his operation and has remained well since. He was last seen in our outpatient department 23

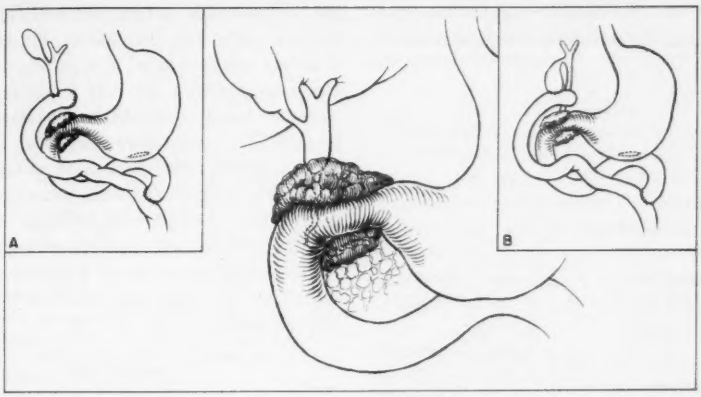

FIG. 4. Carcinoma of the extrahepatic bile ducts: unresectable lesion short-circuited by (*A*) Roux-en-Y choledochojejunostomy and gastroenterostomy (refer to case 4) or (*B*) Roux-en-Y cholecystojejunostomy and gastroenterostomy.

months following surgery, when he was noted to be entirely asymptomatic and without evidence of residual tumor. On pathologic examination, the lesion proved to originate in the biliary duct, although this was not determined until after it was resected.

Case 3 (*see fig. 3*). The patient was a 68-year-old Caucasian man who had been entirely well until July 1958, when he noted the onset of jaundice and pruritis. On July 15, 1958, he was operated upon at another hospital and a small tumor of the common bile duct was discovered. The tumor was biopsied and a diagnosis of adenocarcinoma was established by frozen section. T-tube drainage was instituted. The patient subsequently was referred to the U. C. L. A. Medical Center for definitive therapy. He was asymptomatic at that time and the T-tube was draining well. On July 30, 1958, a cholecystectomy and local resection of the common bile duct was carried out. Continuity was re-established by a Roux-Y choledochojejunostomy. Pathologic examination of the specimen confirmed the presence of an adenocarcinoma arising at the junction of the common bile duct and cystic duct. Postoperatively, the patient developed a right subphrenic abscess which necessitated drainage. He improved steadily after that and was discharged about 5 weeks postoperatively entirely asymptomatic and without jaundice. He was seen last 9 months after surgery; he was well and had no signs of recurrent tumor.

Case 4 (*see fig. 4*). This patient was a 63-year-old Caucasian woman who was admitted on September 16, 1955, with the history of a gradual onset of postprandial fullness and nausea and right upper quadrant abdominal aching pain during the preceding 6 months. She consulted a physician, who found a nonfunctioning gall bladder following oral cholecystography. A cholecystectomy was performed at another hospital 1 month after the onset of symptoms. Several small stones were reportedly found in the cystic duct. The patient's postoperative course was uneventful until about 2½ months later when she complained of generalized pruritis, and within 2 weeks was frankly jaundiced. She was re-explored at the same hospital and a T-tube was placed in the common duct. Bile drainage was apparently satisfactory for about 1 week, at which time it ceased completely. Her jaundice persisted, and 1 week before admission to the U. C. L. A. Medical Center she developed symptoms and signs of cholangitis. The patient was re-explored on September 22, 1955. A mass was noted in the hepatoduodenal ligament which appeared to be partially obstructing the duodenum. Frozen sections of a narrowed segment of the common bile duct revealed adenocarcinoma. A choledochojejunostomy, using a defunctionalized Roux-Y limb of jejunum, was accomplished in conjunction with a gastrojejunostomy. Postoperatively, the jaundice cleared and the patient remained well enough to resume fairly normal activity. She was lost to follow-up 2 months later, at which time she had maintained her weight but complained of anorexia and pruritis. She was not jaundiced when last seen.

RESULTS

The present study concerns 20 cases of primary carcinoma of the extrahepatic bile ducts seen during the past 4 years at the U. C. L. A. Medical Center and in the private practice of one of the

TABLE 1

Carcinoma of the extrahepatic biliary ducts

Number of Cases	Operation and Results	Interval after Operation
9	Pancreaticoduodenectomy	
	Alive and well	7 years, 3 months
	Alive and well	2 years, 1 month
	Alive and well	2 years
	Dead	1 year, 6 months
	Dead	1 year, 2 months
	Dead	11 months
	Alive and well	9 months
	Alive and well	6 months
	Dead	12 days
1	Hepaticoduodenostomy	
	Dead	7 months
4	Stent thru tumor, no resection	
	Alive and well	2 years, 2 months
	Dead	1 year, 3 months
	Dead	6 weeks
	Dead	1 month
1	Biliary-enteric anastomosis with local resection	
	Alive and well	10 months
3	Biliary-enteric anastomosis without resection	
	Dead	8 months
	Dead	2 months
	Dead	2 months
2	Exploration and biopsy	
	Dead	3 months
	Dead	10 weeks

authors (W. P. L.). Of these, 2 patients were explored and only a biopsy taken. The remaining 18 cases were operated upon for palliation or cure. These operative procedures and the results obtained are summarized in table 1.

There were 9 radical pancreaticoduodenectomy procedures performed. One patient succumbed on the 12th postoperative day; 3 others died 11, 14 and 18 months, respectively, after operation; 5 patients are still alive 6 months to 7 years and 3 months without evidence of disease.

A hepaticoduodenostomy was performed at the porta hepatis in 1 patient who survived for 7 months with fair palliation. Simple catheter drainage was instituted in 4 patients. Of these, 2 succumbed within the first 6 weeks, but 1 patient lived over 15 months and another is asymptomatic 26 months after operation. Resection of the lesion and re-establishment of biliary-enteric continuity by a choledochojejunostomy was employed in 1 patient who is living and well 10 months later. Simple short-circuiting of the lesion by choledochojejunostomy was utilized in 3 patients, all of whom were dead in the 8 months after operation.

DISCUSSION

Although the results are largely palliative in this type of surgery, there is still much to be gained in the prolongation of life and in the relief of symptoms by an aggressive surgical approach to this disease. Dennis and Varco[4] and Siler and Zinninger[19] have reported much the same experience as we have had in the management of these cases. The lesions are often slow-growing and death is frequently the result of local obstruction of the extrahepatic biliary tract or duodenal obstruction rather than the effect of widespread distant metastases.

In general it may be said that resection offers the greatest degree of palliation when it can be carried out without too great an immediate operative risk. Resection for *cure* should be attempted under even greater degrees of risk when the alternative leaves little choice. Thus, radical pancreaticoduodenectomy should be employed for any lesion which can be grossly circumscribed by this procedure (fig. 2). We have utilized this operation for localized lesions of the distal end of the common duct. It is not always possible, however, to distinguish a primary carcinoma of the biliary ducts from a carcinoma of the head of the pancreas. A choledochotomy or duodenotomy may be helpful in making this distinction, although frozen sections are notoriously inaccurate in this regard. Our own approach in such a situation is simplified by the fact that we would elect to do a pancreaticoduodenal resection for a localized lesion of the head of the pancreas as well.

If one cannot effect a reasonable attempt at "cure," various procedures of lesser magnitude are available which offer considerable palliation. Resection is attempted where possible (figs. 3 and

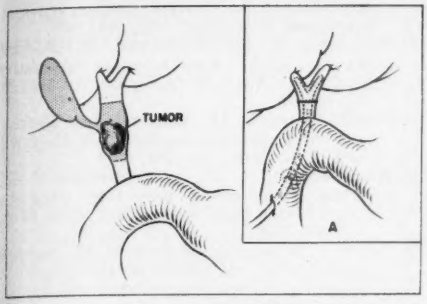

FIG. 5. Carcinoma of the extrahepatic bile ducts: localized tumor of proximal common bile duct. Local resection and cholecystectomy and end-to-end biliary anastomosis.

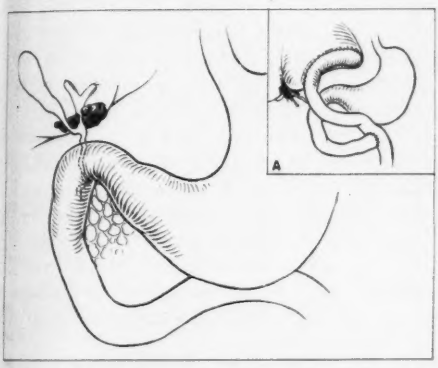

FIG. 6. Carcinoma of the extrahepatic bile ducts: unresectable lesion located below confluence of the right and left hepatic ducts in the hilus of the liver. Biliary decompression accomplished by short-circuiting procedure involving partial resection of the left lobe of the liver and intrahepatic cholangiojejunostomy.

5); short-circuiting operations are considered when the lesion cannot be removed (fig. 4). Decompression procedures are utilized as a last measure. A T-tube or catheter may be literally rammed through a tumor and left in place indefinitely (fig. 1). Intrahepatic cholangiojejunostomy, originally designed for benign biliary stricture, has been employed successfully by some authors in selected patients with slow-growing carcinoma of the extrahepatic biliary ducts (fig. 6).

In our own experience there were only 2 cases, both involving the right and left hepatic ducts high in the hilus, in which we were unable to decompress the biliary tract by some procedure. In every other instance some type of resection, short-circuiting, or decompressing procedure was carried out with only a single operative death for the entire series.

SUMMARY

Carcinoma of the extrahepatic biliary tract is often a slow-growing tumor which is frequently "incurable" from the time the diagnosis is made. Palliation is usually the single most important consideration in the management of these cases. The level of the tumor in the biliary tract determines the operability of the disease and the degree of palliation which may be anticipated. The surgical literature in general presents a pessimistic attitude in regard to the operative management of such patients. It has been the authors' experience that an aggressive surgical approach is not only justifiable but may be very rewarding. Of the 20 cases herein presented, satisfactory biliary decompression was accomplished in 18 with an operative mortality of 5 per cent. Of 9 radical pancreaticoduodenectomy procedures performed, 5 patients are still alive and without evidence of disease 6 months to 7 years and 3 months after operation. Three of these cases have survived over 2 years.

Dr. Harvey N. Lippman
University of California Medical Center
Los Angeles 24, California

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THE CEREBRAL CIRCULATION: THE VARIABILITY OF ITS ADEQUACY AND CLINICAL ASSESSMENT*

W. EUGENE STERN, M.D.

Los Angeles, California

The brain accounts for but 2 per cent of the body weight and yet utilizes 20 per cent of the body's oxygen requirement and receives one-sixth of the normal cardiac output.[3] Since this organ possesses no oxygen reserve, its dependence upon a continuous and adequate flow of oxygenated blood is at once established. Interference with this supply can be produced by disease or, in a premeditated fashion, by the surgeon in his management of intracranial lesions. At a time when the surgeon's interest is being directed toward re-establishing blood flow to the brain by cervical carotid artery thromboendarterectomies, a discussion of factors which contribute to the variability in the functional adequacy of cerebral circulation in the face of obstruction in the main supply may be pertinent. Observations during the induction of arterial insufficiency in the management of intracranial vascular lesions and case presentations documented in brief may contribute to our understanding of these factors.

ANATOMICAL FACTORS

Cervicothoracic Supply

The anatomy of the vessels in this region is reasonably constant. There are, however, recognized differences in the size of the two vertebral arteries which form the basilar artery. There are also documented but apparently very rare examples of the congenital absence of either one or both common carotid arteries in man. The importance of knowledge of such variations in a given case is obvious when the surgeon attempts to assess the importance of each remaining component to cerebral blood supply. The relative importance of the vertebrobasilar system on the one hand and the carotid systems on the other will depend on whether the circle of Willis, which receives them, is of the usual adult pattern (fig. 1) or varies in the size or existence of all its parts.

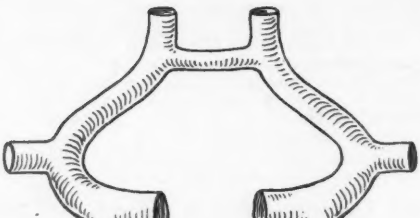
Circle of Willis as shunting or distribution system. The arterial circle at the base of the brain possesses no important intrinsic capacity to shunt selectively or pump; it is a passive distributing complex, the potential of which may not be realized until one of the major input vessels is obstructed. The first two cases introduce the problem of assessment of adequate circulation.

Case 1. A 28-year-old bank teller suffered a spontaneous subarachnoid hemorrhage 19 days before hospital admission. He possessed a complete left third cranial nerve paralysis and harbored a saccular aneurysm arising on the supraclinoid portion of the internal carotid artery. Cerebral angiography demonstrated ipsilateral middle and anterior cerebral arterial filling on the diseased side and bilateral filling of the anterior cerebral arteries from the normal side. Such data gave evidence of the patency of the anterior portion of the circle of Willis by virtue of the common filling of at least one anterior cerebral artery from each carotid injection. Left common carotid artery ligation was tolerated well and was followed 3 weeks later by internal carotid artery occlusion. The patient became suddenly aphasic and hemiplegic 48 hours after irreversible occlusion. The hemiplegia rapidly improved, but the speech deficit remained troublesome for several years.

Why did this patient become hemiplegic? To answer this with certainty is not possible. On anatomical grounds, the integrity of the anterior half of the circle of Willis is the anatomical substrate of the most important potential collateral supply when one carotid artery is occluded, but that its mere existence is in itself not enough for adequate functional collateral is obvious. It is also clear that supply from the posterior half of the circle was also inadequate. So also was whatever blood that may have been coming from the external carotid artery via back flow from its midline anastomoses with its opposite fellow.

Case 2. A 58-year-old laborer suffered right-sided head pain and dropping of his right eyelid during the week before hospital admission. A

* From the Department of Surgery, Division of Neurological Surgery, University of California Medical Center, Los Angeles, California.



NORMAL CIRCLE OF WILLIS

FIG. 1. The familiar diagrammatic pattern of an intact, adult circle of Willis. The side-to-side communicating channels are especially constant and competent in the anterior portion of the complex. Note also the potential but small communications between back and front.

complete third nerve paralysis existed on the right, and, as in the patient of case 1, a saccular aneurysm of the right internal carotid artery was visualized in the supraclinoid location with adequate ipsilateral anterior cerebral artery filling. Once again both anterior cerebral arteries were visualized when the normal carotid system was injected. Acute cervical carotid artery occlusion produced an immediate drop in internal intracarotid pressure from 125/75 to 86/62 mm. Hg, indicating a residual pressure exceeding 60 per cent of normal in both systolic and diastolic components. Both angiographic data and pressure data indicated a functioning circle of Willis[1] and therefore the right internal carotid artery was occluded, stepwise, over 4 days. Total occlusion was only tolerated for 30 hours at which time sudden confusion and left-sided hemiparesis developed. Clamp release within 10 minutes was followed by complete recovery from deficit within 4 hours. Total occlusion was subsequently accomplished and well tolerated.

Why did this patient become paralyzed? The circulation pattern anatomically was similar to the first case. In addition, there were data on the residual arterial pressure in the carotid system above the site of occlusion. Experience has demonstrated that a reduction of pressure of more than 60 per cent or to an absolute figure of 50 mm. Hg or below will be associated with frequent complications of insufficiency.[7] In this patient the residual pressure seemed compatible with safe occlusion. It may be noted that it was not until total occlusion was reached that symptoms followed, and at about the same time delay after complete shut-off, as in case 1. The rapidity of reversal of paralysis after clamp release speaks strongly against a propagating thrombosis or embolization incident to occlusion. It is important to recognize this point because the absence of an anatomical lesion, as suggested here, means that dynamic factors, in addition to the surgeon's clamp, contributed to the circulatory failure. Examination of the artery in the neck 3 weeks later revealed the vessel to be totally occluded from the clamp to the base of the skull, and yet no further sequelae occurred. The sudden episode of hemisphere dysfunction most probably represented a functional type of ischemia; the hemisphere was transiently dependent upon the integrity of its own ipsilateral carotid circulation, but, fortunately, not permanently dependent.

The delay in onset of paralysis after total occlusion needs emphasis. It is to be remembered that the brain cannot store up oxygen against future need, and hence its normal function for 30 hours after occlusion indicates that for that time it was independent of the occlusion in the diseased carotid artery. It is clear that the angiographic data as well as the pressure data were in themselves insufficient to provide ample assessment of the status of the circulation. These limitations have been pointed out well by Strobos and Mount[6] and Stern.[5]

This case study contains a clue to the etiology of the transient and often reversible attacks of hemisphere dysfunction frequently associated with carotid system occlusive disease.

Further clinical evidence of the competency of the circle as a distribution mechanism is obtained from the next case.

Case 3. A 37-year-old man suffered a third cranial nerve paralysis and subsequently a subarachnoid hemorrhage from an aneurysm in the same location as that of the two previous cases; namely, on the supraclinoid portion of the internal carotid artery. Common carotid artery occlusion was well tolerated and no neurologic deficit resulted. The patient continued to suffer head pain which suggested activity with the aneurysm, and an intracranial approach was effected. The lesion

defied direct ligation, and therefore a distal occlusion of the carotid artery was decided upon. The cervical internal artery had been demonstrated to be occluded to a solid cord, but intracranially the vessel had blood in it as did the aneurysm. Intracranial carotid occlusion was followed by upper extremity monoparesis and dysphasia.

The occlusion had interfered with the previously adequate irrigation of the ipsilateral hemisphere with blood from the rest of the circle of Willis, and it is probable that the intracranial ligation precipitated thrombosis into the circle, thereby interfering with middle cerebral artery supply to speech and arm areas. The circle could no longer distribute blood in the face of cervical occlusion because its own integrity had been compromised.

External to internal carotid system anastomosis. Anastomoses from external to internal carotid systems may be functionally significant. The following case history is an example in point at least insofar as it establishes the anatomical features as potential sources of blood to the compromised system.

Case 4. A 49-year-old manufacturer was admitted to the hospital in December 1955 with a 2 months' history of transient disturbances of unconsciousness and several dozen intermittent episodes of dysfunction involving the right upper extremity. A fluctuating monoparesis and mild dysphasia were noted, together with an arterial hypertension of 198/110. Internal carotid artery thrombosis was diagnosed and confirmed angiographically. The angiogram demonstrated the striking patency of the anastomotic connections between ipsilateral external carotid system via the ophthalmic artery. At the time of thromboendarterectomy,* when both common and internal carotid arteries were occluded, there were strong residual pulsations in the external carotid branches. Whether these pulsations reflected back flow, or, as is more probable, crossover from the rich bilateral cervical anastomoses could not be ascertained. The relative contribution to the ischemic hemisphere through the anterior part of the circle on the one hand and the external carotid anastomosis on the other could not be established, but the implication is clear that the latter may have played a significant role.

This case focuses attention again upon the pattern of cervical supply in the face of interference and the occasional importance of external carotid flow.

Anastomoses above circle of Willis. Anastomoses at the suprawillisian level, that is to say between various branches of the circle at a level above their origin, will be of considerable importance if occlusive processes include portions of the main trunks of anterior, middle or posterior cerebral arteries. The next case history presents an illustrative example of such anastomoses.

Case 5. A 43-year-old man suffered a spontaneous subarachnoid hemorrhage from an aneurysm located at the origin of the anterior and middle cerebral arteries on the left side. He was hemiplegic and aphasic. Intracranial clipping was attempted, but because the neck of the lesion fractured and because blood was reaching the aneurysm from retrograde flow of considerable proportion, it was necessary to occlude the internal carotid artery, then the anterior cerebral artery, and finally the middle cerebral artery to control the bleeding. Postoperatively, his neurologic deficit was unchanged. Angiograms following operation revealed that the involved hemisphere was served by blood from the opposite side via the circle of Willis, but more importantly they revealed that the territory of the involved middle cerebral artery was served by flow through channels which connected the middle cerebral branches with anterior and posterior cerebral branches ipsilaterally (and possibly contralaterally) above the level of the circle. The capacity of such transmeningeal anastomoses to contribute significantly may explain the observed preservation of important neurologic function.[4, 8]

These illustrative examples of vascular connections recapitulate recognized anatomical facts of sources of blood which may serve the brain to which a major artery is obstructed. Figure 2 presents a graphic summary of the major possibilities (1) from across the intact circle of Willis, (2) from external to internal carotid systems, and (3) from suprawillisian anastomoses, irrespective of whether they are functional. In a given case the role they may play needs to be given recognition.

TEMPORAL FACTORS

The tempo of the process which interferes with flow within one of the main channels of supply to the brain may to some degree govern the tolerance through whatever adaptive mechanisms are available. Many examples are at hand of long-

* In conjunction with Dr. Jack A. Cannon.

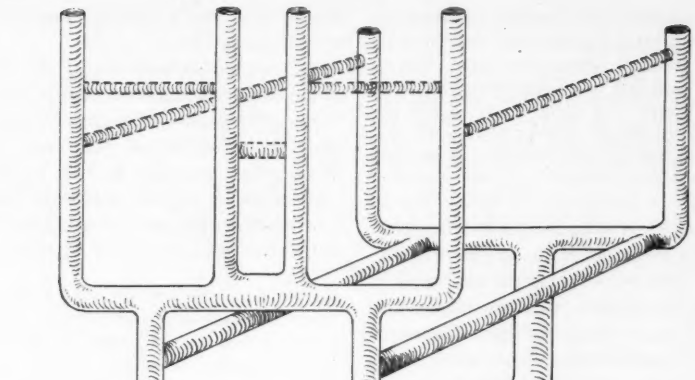


FIG. 2. Diagrammatic representation of major potential shunting channels between internal and external carotid arteries and various parts of the circle of Willis and between the branches above the circle. The basic anatomy appears as *solid shaded* channels; the potential channels are *dotted*. The base of the skull is represented by the bone at the *asterisk*.

standing carotid artery occlusion which have remained symptomless, testifying to the probable role of time in permitting the anatomical channels which exist to become functional. Although data derived from studying the effects of chronic obliterative disease of parts of the cerebral circulation are valuable, caution must be used in reasoning from these to the problems confronting the surgeon when acute occlusion is required in the treatment of aneurysms and similar lesions. It is of interest that the acute reduction of intravascular pressure wrought by carotid occlusion and measured by retinal ophthalmodynamometry may in certain patients be observed to be reestablished in a matter of days to approach preocclusion pressures. However, such short time of reduced pressure and presumably also reduced total flow may be sufficient for neural dysfunction.

FUNCTIONAL FACTORS

Important as these anatomical and temporal considerations are, the foregoing cases clearly point to other equally important influences governing adequate flow. Kety[3] has admirably elucidated many of these. It is the study of human case material in its conscious state with the observation of clinical responses which, better than any pressure data, flow data, or angiographic data, will give the truest assessment of the adequacy of circulation. There are probably several mechanisms for the interesting clinical state of carotid arterial insufficiency manifested by what Hunt[4] called "cerebral intermittent claudication" and illustrated by case 4. Observation of a patient undergoing acute occlusion of a cervical carotid artery sheds some light on at least one mechanism whereby this is produced.

Case 6. A 40-year-old secretary was admitted to the hospital with a history of sudden hemicranial pain and transient ipsilateral ptosis. Angiography demonstrated an aneurysm of the intracranial internal carotid artery near its emergence from the cavernous sinus. Bilateral studies angiographically revealed no crossover from the unaffected side to the symptomatic side even with ipsilateral manual carotid compression at the time of contralateral injection. An adjustable Selverstone clamp was applied to the ipsilateral internal carotid artery. The intravascular pressure in this artery was noted to fall to zero when the common carotid artery was occluded. Although the vessel was occluded over 4 days, no adverse effects were experienced until 7 hours after complete occlusion, at which time contralateral arm numbness and weakness supervened. Release of the clamp was followed by the disappearance of the numbness and return of strength. The deficit could be reproduced by retightening the clamp. Again, over the succeeding 4 days the vessel was fully occluded and the retinal artery pressures fell from equal levels on the two sides to 35/30 on the occluded side and 130/60 on the intact side (here is another method alluded to above of clinical assessment of circulation). The brachial pressure was 145/75 mm. Hg. Within 3 hours a return of numbness and clumsiness in the left arm was observed. Carbon dioxide inhalations were given, and the severity of the numbness and weakness varied in a remittent fashion. Release of the clamp was deemed advisable after an additional 3½ hours. With this evidence from clinical trial it was decided to leave the vessel subtotally occluded with a residual retinal artery pressure of 45/30 as compared with 130/60 on the opposite, intact side. Angiography in a succeeding 4 days revealed no crossover from the intact side to the occluded side.

This patient seemed to require that a certain minimum of blood be furnished by way of the ipsilateral carotid artery. Subtotal, acute occlusion gave rise to no symptoms or deficit, whereas total occlusion produced a fluctuating, remittent picture readily reversed by re-establishing only a fraction of normal flow. It is clear that the remittent nature of the deficit during total occlusion was not related to fluctuation in the degree of obstruction but rather dependent upon other dynamic factors. Probably the most important of these, and insufficiently emphasized, is the variability in mean systemic arterial blood pressure upon which the maintenance of cerebral blood flow is vitally dependent. The variations in pressure of this particular patient during a 21-day period of 1 to 2 hourly recordings was 185 to 115 mm. Hg systolic and 108 to 70 mm. Hg diastolic. It can be appreciated that a compensatory blood supply to a cerebral hemisphere which is already compromised by ipsilateral carotid artery occlusion might be adequate in certain of these ranges of systemic blood pressure, although inadequate to preserve function normally in other ranges. All manner of influences upon the systemic pressure might therefore be reflected in the sensitive barometer of cerebral function. Such an explanation is, in all probability, an oversimplification of a complex process in which changes in blood pCO_2 and pO_2, total circulating blood volume, oxygen carrying capacity, viscosity, intracranial pressure and so forth are only superficially considered. Studies of patients such as these lead to the opinion that the intermittent and remittent nature of the clinical manifestation of carotid system insufficiency is not due to a reversible structural change in the vessel but often signifies a fixed if not progressive occlusion of one or more of the major vessels of supply. The degree of partial occlusion necessary to be clinically significant will probably differ from case to case depending upon the variables suggested in the foregoing case studies, but it is probable that it must approach subtotal occlusion.

SUMMARY AND CONCLUSIONS

The study of patients undergoing elective vascular occlusion for intracranial processes such as aneurysms sheds light on the dynamics of cerebral circulation. The clinical assessment of the circulation in any given case requires an understanding of possible anatomical variations from the normal pattern. The determination of the anatomical pattern is elucidated by bilateral carotid angiography and vertebral angiography, incorporating the techniques of contralateral carotid compression during ipsilateral injections. Determination of retinal artery pressures, with and without manual cervical occlusion, offers an additional tool in assessing functional adequacy. Intracarotid pressure recordings during occlusion of the surgically exposed vessels in the neck again adds to the surgeons' knowledge of a given case. However, rather than trying to equilibrate too rigidly such data with adequacy or inadequacy of flow, the surgeon should recognize that it is the clinical behavior and performance during and after reversible occlusion which contributes the most reliable information to the assessment

of the adequacy of the circulation. There is clinical evidence to support the concept that the clinical picture of intermittent carotid artery insufficiency is produced by fluctuating functional factors of pressure and flow superimposed upon severe, fixed subtotal to total occlusion of one or more major feeding channels. The next obvious question to raise is what degree of partial occlusion is clinically important and therefore might be justifiable of surgical correction.

University of California Medical Center
Los Angeles 24, California

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THE ELECTROENCEPHALOGRAPHIC EFFECTS OF ARRESTED CIRCULATION DURING HYPOTHERMIA

VERNE L. BRECHNER, M.D., EVA M. KAVAN, M.D., ROBERT W. BETHUNE, M.D., ROBERT O. BAUER, M.D., AND JOHN B. DILLON, M.D.

Los Angeles, California

INTRODUCTION

Nine years have elapsed since introduction of the techniques of intracardiac surgery during temporary circulatory arrest and induced hypothermia.[3] During this time an extensive literature has evolved concerning electrocardiographic and other physiologic alterations accompanying such procedures. Although the central nervous system is readily recognized as being vulnerable to the effects of hypothermia and occluded circulation,[4, 7, 10, 14] little information has been published regarding alterations of human cerebral electrical activity during these operations.[11]

The purpose of this study is to investigate the variations in human electrocortical activity resulting from circulatory arrest during induced hypothermia, and to determine whether the electroencephalographic patterns provide information immediately useful to the anesthesiologist in managing the problems at hand.

METHOD

In the past year 28 patients subjected to circulatory arrest during induced hypothermia for the repair of various cardiac defects were monitored electroencephalographically. The circulation was arrested twice during the same operation in 2 patients. Thus, 30 records of electroencephalographic patterns throughout and following total occlusion of the circulation were obtained. Pertinent data concerning diagnoses, anesthetic and operative procedures are presented in table 1.

Electrocortical activity was recorded with either the Edin or the GME operating room electroencephalographs employing a pair of needle electrodes placed frontocoronally 2 cm. lateral to the sagittal sinus. A paper speed of 1.5 cm. per second and a gain of 100 μv. per centimeter was used with each record. Electroencephalographic activity was recorded periodically during induction of hypothermia and the initial phases of the operation. One minute before circulatory arrest the electroencephalograph was turned on and continuous recordings were obtained throughout the remainder of the operation or until the return of electroencephalographic patterns similar to those observed before occluding the circulation. Postoperative electroencephalograms were recorded with the 8-channel Grass machine in 1 patient whose electrocortical activity remained markedly depressed at the end of the operation.

Hypothermia in ranges of from 28.5–33.5°C. rectal temperature was induced by means of the Therm-O-Rite machine and cooling blankets. Rectal temperature was measured with a thermistor inserted approximately 6 inches past the anus. Occult shivering, as indicated by course fibrillatory activity of the EKG baseline, was controlled by intravenous injections of curare. Phenothiazines were not employed at any time.

Cyclopropane or a mixture of cyclopropane and diethyl ether was employed as the anesthetic. The plane of anesthesia was kept as light as possible before arresting the circulation, and electroencephalographic patterns lighter than plane 3 of Faulconer and Possati's classification[5, 6, 13] were recorded in all cases. Anesthetic concentrations in alveolar gas or arterial blood were not measured. Upon onset of circulatory arrest, administration of all anesthetics was discontinued and not resumed until the patient moved following restoration of circulatory continuity. With the exception of the intermittent recordings before circulatory arrest, all records discussed in this paper, therefore, were obtained while the anesthetic administration was discontinued.

Endarterial pressure was monitored with a Stratham strain gauge, the tranducer recording from a catheter inserted in the brachial or radial artery.

Postoperatively the patient's mental behavior was closely observed, particular attention being given to the occurrence of restlessness and disorientation, response to questioning, and memory of events before the operative procedure.

TABLE 1

Tabulation of diagnosis and procedures

Patient	Age	Anesthetic Agent	Diagnosis	Rectal Temp.	Duration of Arrest	Time Onset Cont. Activity	Remarks
				°C.	*sec.*	*min.*	
L. G.	10	Cyclo	IASD*	30.5	455	35.0	Restless and disoriented first 6 postoperative hours (−)†
G. H.	15	Cyclo	IASD	30.5	390	21.0	Alert postoperative
M. D.	5	Cyclo	IASD	30.0	270	2.0	Alert postoperative
S. M.	13	Cyclo	IASD	32.0	280	2.33	Alert postoperative
W. G.	30	Cyclo	IASD	30.0	480	29.0	Alert
M. K.	54	Cyclo	Aortic valve stenosis	30.5	Circ. not restored	None	Died in operating room
N. E.	11	Cyclo	IASD	31.5	240	2.0	Alert
J. K.	6	Cyclo and ether	IASD	30.5	385	13.0	Alert
		Cyclo and ether	IASD	30.5	375	12.0	Alert
L. C.	4	Cyclo	Pulmonary stenosis	31.5	360	12.0	Alert
L. W.	8	Cyclo	IASD	31.5	210	3.0	Alert
S. M. O.	5	Cyclo	IASD	30.5	330	2.6	Alert
K. O.	13	Cyclo	IASD	32.5	270	2.0	Alert
R. I.	4	Cyclo	IASD	31.0	290	2.0	Alert
G. L.	49	Cyclo	Aortic stenosis	32.5	140	1.1	Alert
M. F.	15	Cyclo	IASD	32.0	390	56.0	4-Min. manual systole, alert (•)
I. C.	34	Cyclo and ether	IASD	31.5	555	90.0	File pattern after circulation restored, restless and disoriented first 24 hours (•)
A. S.	35	Cyclo and ether	IASD	30.5	320	3.0	Alert
M. S.	3	Cyclo and ether	IASD	32.5	320	11.0	Alert
R. R.	12	Cyclo	IASD	29.5	400	14.0	Alert
T. Y.	3	Cyclo and ether	Pulmonary valve stenosis	31.0	290	3.0	Alert
		Cyclo and ether		31.0	155	1.0	Alert
S. N.	21	Cyclo and ether	IASD	29.5	285	6.0	Alert
J. N.	33	Cyclo	IASD	31.0	355	41.0	Died, ventricular fibrillation after circulation restored (×)
R. S.	4	Cyclo	IASD	29.0	460	17.0	Alert
J. R.	5	Cyclo	IASD	28.5	240	1.0	Alert
S. N. E.	9	Cyclo and ether	Pulmonary stenosis	33.5	195	1.3	Alert
M. M.	8	Cyclo	IASD	30.5	190	1.0	Alert
P. P.	7	Cyclo and ether	IASD	31.5	400	20.0	Alert
D. C.	46	Cyclo	Aortic stenosis IASD	30.5	720	None in 75 min.	Markedly disoriented first 24 postoperative hours

† Keys (−) (⋆) (•) (×) identify patients in figure 1.

* Intra-atrial septal defect.

RESULTS

Electroencephalographic patterns before circulatory arrest. As stated previously, electroencephalographic patterns lighter than Faulconer's pattern 3 were maintained during the administration of anesthesia. As hypothermia increased it was generally observed that less anesthetic was needed to maintain a constant state of cerebral depression as recorded by the electroencephalogram.

Electroencephalographic patterns during circulatory arrest. The electroencephalographic response to circulatory arrest was dramatic. Within a few seconds of clamping the venae cavae, and simultaneously with a reduction of endarterial blood pressure to 35–45 mm. Hg, a marked slowing of frequencies and an initial increase in amplitude of the brain waves appeared. The amplitude then rapidly decreased until an isoelectric pattern was recorded. The time lapse between inflow tract occlusion and onset of electrical silence varied from 8 to 46 sec., averaging 24 sec. When circulation was occluded by cross-clamping the aorta, the onset of an isoelectric pattern was accelerated, occurring in from 6 to 10 seconds. There was no correlation between rectal temperatures and time lapse between circulatory arrest and onset of electrical silence (*i.e.*, electrical activity did not persist longer at cooler temperatures), nor could the patients' ages be corrlated with persistence of electrocortical activity following circulatory arrest.

Nine patients developed a curious type of electrical activity after the electroencephalographic patterns had become otherwise isoelectric (figs. 2*D* and 3*F*). This activity persisted for 20 to 60 sec. and consisted of very low voltage (10 μv. or less) rapid frequency (25 cps or more) oscillations of the baseline. There was no correlation between occurrence of this phenomenon during circulatory arrest and electroencephalographic patterns evolving after restoration of circulation nor in the postoperative condition of the patient.

Electroencephalographic patterns following termination of circulatory arrest. Electrocortical activity did not return immediately upon termination of circulatory arrest; and the time lapse between restoration of circulation and onset of electrical activity seemed to be influenced by the duration of occluded circulation, electrical silence persisting longer in patients subjected to more prolonged periods of arrest.

Semilog graphs were drawn correlating duration of circulatory arrest with the log of time elapsed between restoration of circulation and onset of the following electrocortical activities: (1) first electrocortical activity; (2) first wave form of 100 μv. amplitude; (3) continuous activity of wave forms greater than 100 μv.; (4) first frequencies faster than 4 cps; (5) continuous activity of frequencies faster than 4 cps; (6) continuous electrocortical activity of any type.

Of the six graphs, the one correlating duration of circulatory arrest with the log of time lapse until onset of continuous activity of any type showed the best grouping (fig. 1). The regression line calculated for this graph had a slope of 1.23 per cent change for each second of arrested circulation with a reliability figure of 0.197 (80 per cent of variables altering slope accounted for by regression on duration of occluded circulation alone), suggesting that this time lapse is a function of duration of circulatory arrest.

The plotted points of 2 patients (M. F. and J. N.) lie well to the left of the regression line (time lapse between restoration of circulation and

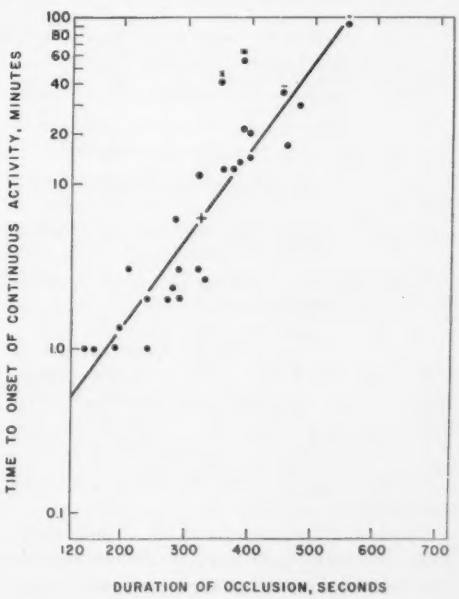

FIG. 1. Correlation of duration of circulatory arrest to log of time lapse between restoration of circulation and onset of continuous activity during hypothermia. See table 1 for keyed patients.

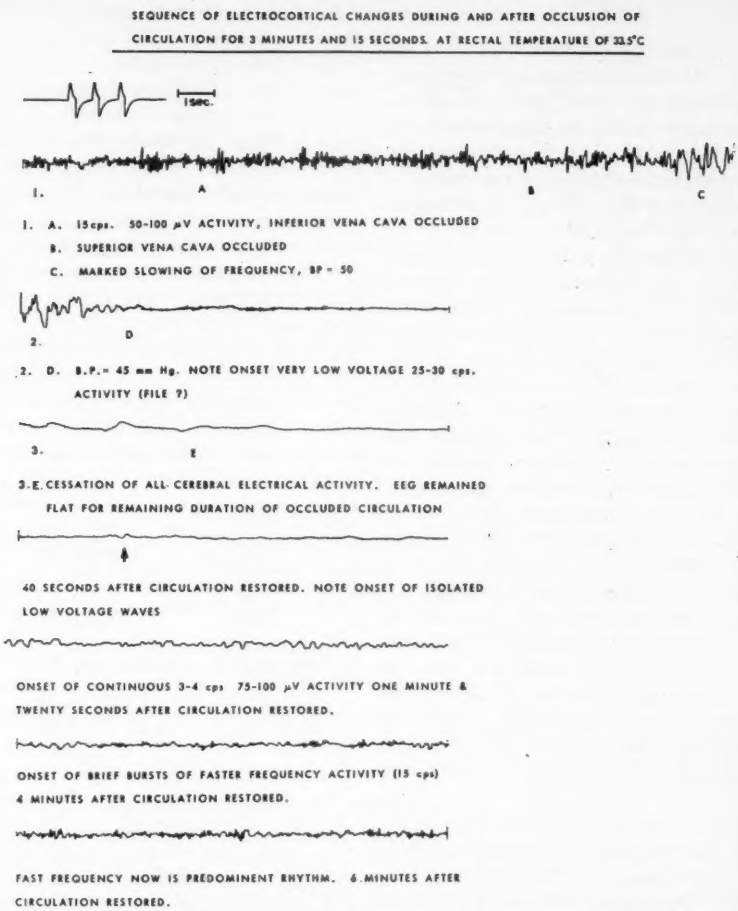

FIG. 2. Electroencephalographic record typical of that seen after relatively brief period of circulatory arrest during hypothermia.

onset of continuous electrical activity was greater than expected from duration of circulatory arrest). These patients developed ventricular fibrillation after restoration of circulation and thus possibly suffered an additional period of inadequate circulation after circulatory continuity was restored.

The data of 2 other patients (D. C. and M. K.) could not be plotted, since continuous activity did not return during the period of electroencephalographic monitoring in the operating room. Both of these patients suffered severe cortical insults and will be discussed in the following paragraphs.

The duration of arrested circulation also influenced the type of electroencephalographic patterns seen upon termination of electrical silence. Patients subjected to relatively short periods of circulatory arrest (less than 7½ min.) initially developed either bursts or continuous activity of slow low voltage (1 to 2 cps, 50 μv.) wave forms which quickly progressed to faster frequencies and higher voltages. Thus, once electrocortical activity returned, patterns of decreasing cerebral depression rapidly ensued. All of these patients with rapidly returning cerebral activity were awake and alert at the termination of operative procedures. They were calm and well

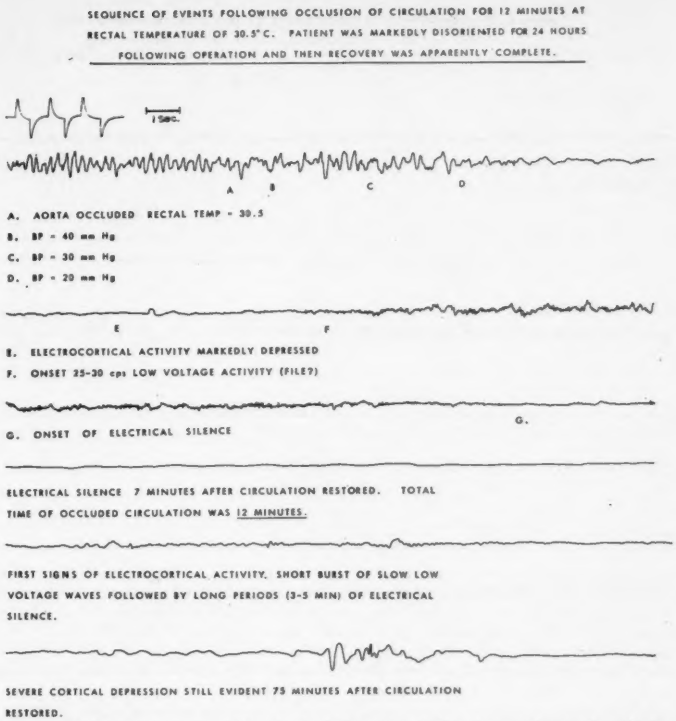

FIG. 3. Electroencephalographic record typical of that seen following prolonged periods of circulatory arrest during hypothermia.

oriented during the postoperative period, retained memory for events before induction of anesthesia, and responded intelligently to questioning. The following case is typical of this group of patients.

S. N. E. (fig. 2), a 9-year-old boy with pulmonary stenosis, was cooled to a rectal temperature of 33.5°C. and subjected to circulatory arrest of 3 min. 15 sec. while the defect was repaired. The electrocortical silence present throughout the period of occluded circulation persisted for 40 sec. following restoration of circulation. Isolated low voltage wave forms then appeared and progressed to continuous 3 to 4 cps activity 1 min. 20 sec. after circulatory arrest was terminated. Voltages and frequencies continued to increase until a pattern similar to that before circulatory arrest was recorded, 6 min. following restoration of circulation. The postoperative course was uncomplicated.

The succession of electrocortical events followed a different pattern in 3 of the 4 patients subjected to circulatory arrest of more prolonged duration than 7½ min. In these patients, once electroencephalographic activity reappeared (1 to 2 cps, 50 μv.), it failed to progress into patterns of faster frequency and higher voltages and repeatedly lapsed into prolonged periods (5 to 10 min.) of electrical silence. The following case illustrates the electroencephalographic events resulting from prolonged circulatory arrest.

D. C. (fig. 3), a 46-year-old woman with aortic stenosis, was subjected to circulatory arrest of 12-min. duration at a rectal temperature of 30.5°C. Following restoration of circulation, electrocortical activity remained silent for 13 min. At that time short bursts of slow low voltage waves (1 to 2 cps, 50 μv.) appeared. Although the voltage of wave forms gradually increased to 100 μv., electrical activity was still occurring in bursts of slow wave forms (1 to 2 cps) separated by long periods of electrical silence 75 min. after circulation was restored. She was markedly disoriented and restless during the first 24 postoperative hours. An electroencephalogram taken several hours postoperatively revealed 4 to 7 cps activity in all

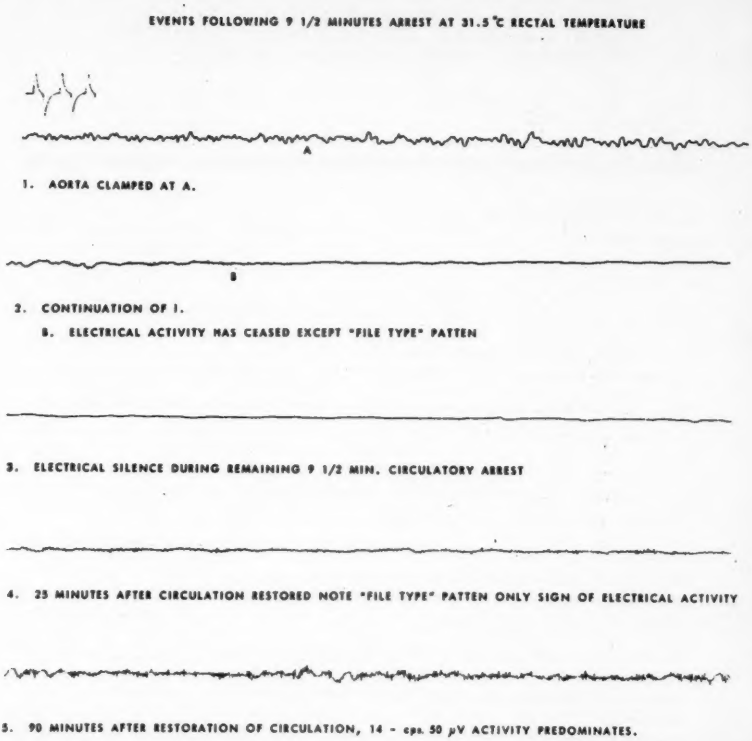

FIG. 4. Electroencephalographic record of "file type" pattern during recovery from circulatory arrest during hypothermia.

leads. On the 1st postoperative day she became oriented and rational, and a repeat electroencephalogram showed a dominant rhythm of 7 to 8 cps. These findings indicated moderately severe diffuse brain damage of a temporary nature. She eventually recovered completely and was able to return to her occupation as a waitress.

Three patients (M. F., J. N. and M. K.) developed ventricular fibrillation when restored to their own circulation. One of these, M. F., was defibrillated after 4 min. of manual systole and survived without complication. The other 2 died in the operating room, after repeated episodes of ventricular fibrillation. In these 3 patients cerebral circulation might not have been completely adequate throughout the period of manual systole, and it is impossible to determine, therefore, the actual duration of functional circulatory arrest. They developed electroencephalographic patterns characteristic of prolonged circulatory arrest just described.

Another patient, I. C., subjected to 9 min. 15 sec. of circulatory arrest, developed a pattern of rapid frequency (25 cps or more), very low voltage (10 μv. or less) oscillation of the baseline after restoration of circulation (fig. 4). Such activity was similar to the patterns described previously in 9 patients during circulatory arrest. This patient was restless and disoriented during the first 24 postoperative hours, but eventually recovered completely.

Effect of repeated circulatory arrest. Two patients (J. K. and T. Y.) were subjected to planned circulatory arrest twice during the same operative procedure.

J. K. (fig. 5) had a large intra-atrial septal defect which could not be completely closed during an initial circulatory arrest of 6 min. 25 sec. The heart was therefore closed and circulation re-established. Within 13 min., continuous electrocortical activity was recorded and patterns similar to those before circulatory arrest appeared 8 min.

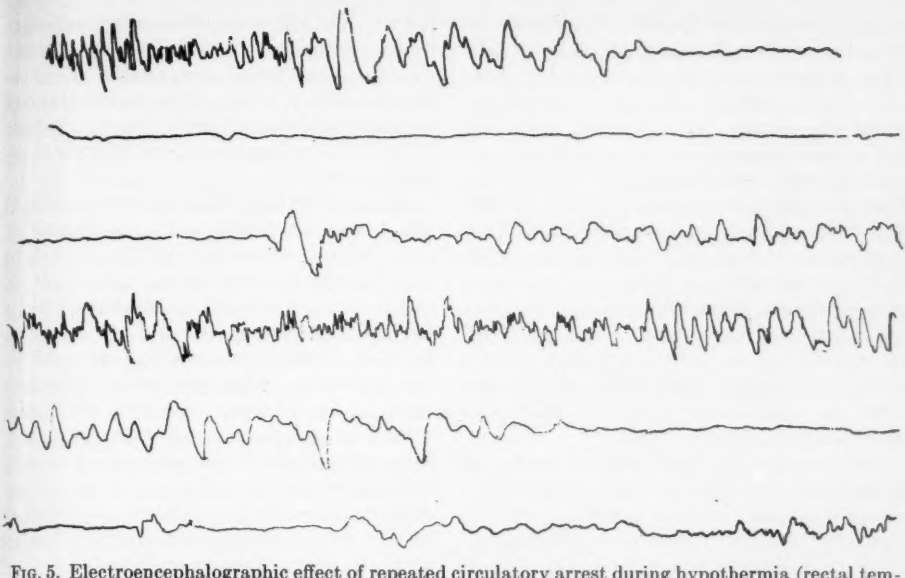

FIG. 5. Electroencephalographic effect of repeated circulatory arrest during hypothermia (rectal temperature, 30.5°C.). *Line 1*, onset of electrical silence following inflow tract occlusion. *Line 2*, continuing electrical silence during 6 min. 25 sec. of circulatory arrest. *Line 3*, return of continuous activity 13 min. following restoration of circulation. *Line 4*, EEG similar to preocclusion pattern 21 min. following restoration of circulation. *Line 5*, circulation reoccluded (6 min. 15 sec. duration). *Line 6*, onset continuous activity 15 min. following restoration of reoccluded circulation.

later. The circulation was then reoccluded for 6 min. 15 sec. while the repair was completed. Return of electrical activity following the second arrest was as rapid as the recovery following the first occlusion; thus, although the total duration of arrested circulation was 12 min. 40 sec., electrocortical function was depressed no more than would be expected from a short period of interrupted circulation. He was calm, alert and well oriented on emergence, in a sharp contrast to the postoperative condition of the patient (D. C., fig. 3) previously discussed who was arrested for 12 consecutive min.

The other patient undergoing 2 episodes of circulatory arrest (T. Y.) had pulmonic valvular stenosis. Following the first surgical attack during 4 min. 50 sec. of arrested circulation, the pressure gradient across the pulmonic valve was unaltered. When electrocortical activity had returned to the preocclusion level, circulation was rearrested for an additional 2 min. 30 sec. while the pulmonary valve orifice was widened. Continuous electroencephalographic activity returned within 3 min. of re-establishing the circulation following both episodes of arrest, and the postoperative course was uncomplicated.

Influence of body temperature and age on electroencephalographic effect of circulatory arrest. Rectal temperatures at the moment of circulatory arrest varied from 28.5 to 33.5°C. The effect of different temperatures on the relations between duration of circulatory arrest and log of time lapse to onset of continuous electrical activity was investigated by comparing the regression line from 6 patients whose temperatures were below 30°C. to the line from 9 patients with temperatures above 31.5°C. No significant difference could be found.

A similar procedure employed to compare the electroencephalographic response of children to that of adults also failed to show any significant difference.

DISCUSSION

Many of our observations are in agreement with the findings of other authors. The appearance of electrical silence soon after circulatory arrest during hypothermia in humans has been reported by Merlis,[11] and in monkeys by McMurrey and associates.[12] The observation that the time lapse between occlusion of the circulation and onset of electrical silence did not vary in relation to depth of hypothermia, is also in agreement with McMurrey's animal experiments. Gunter and associates[9] observed, however, that

increasing degrees of hypothermia delayed the onset of electrical silence due to anoxia in cats. These animals were ventilated artificially with pure nitrogen and the circulation was not mechanically occluded. Thus, vascular stagnation and tissue hypercarbia were prevented and anoxia was the sole cerebral insult. It has been reported[12] that even a markedly reduced cerebral blood flow will sustain electrocortical activity in hypothermic animals, the electrical silence following circulatory arrest being more the result of accumulated metabolites due to circulatory stagnation than to anoxia *per se*. In any event, the sequence of events following circulatory arrest during hypothermia seems to differ from that seen when the animals suffer a purely anoxic insult with an intact circulatory system.

The appearance of fast frequency (25 cps or more), very low voltage activity as the electroencephalographic patterns became isoelectric soon after circulatory arrest deserves some comment. Frequencies as fast as 50 cps with voltages as low as 5 μv. were reported during cardiac arrest in normothermic humans by Bellville[1] and Howland[2] and Grönqvirst and associates.[8] These authors described this activity as a "file pattern" and thought that it was an agonal type of electroencephalographic activity. The electroencephalographs used in our investigation employ a 30 cps cut-out filter. Frequencies as fast as 50 cps, therefore, would not be recorded. We feel, however, that the fast frequency, low voltage patterns were of the "file" type. The appearance of this file type activity during circulatory arrest in 9 of our hypothermic patients was not correlated with any adverse electroencephalographic or clinical events. The sole patient exhibiting this type of activity after circulation was restored (I. C.), however, was markedly disoriented and restless for the first 24 postoperative hours, and the duration of circulatory arrest (9½ min.) had been prolonged. We feel, therefore, that the occurrence of a filelike pattern after restoration of the circulation is of prognostic significance.

Although other investigators[2, 12, 15] have observed a rough correlation between duration of circulatory arrest and prolongation of electrical silence following restoration of circulation, they have not found as close a relationship as we have by using onset of continuous activity as the end point. Although a reliability figure of 0.193 (80 per cent) still allows a relatively wide grouping of points around the regression line, we feel that considering the clinical circumstances of our observations the time lapse between restoration of circulation and onset of continuous activity may be considered a function of the duration of circulatory arrest.

It is apparent that a time lapse greater than 30 min. is associated with undesirable clinical results. Of the 6 patients not exhibiting continuous electrical activity within 30 min., 3 (I. C., D. C., and L. G.) were agitated and disoriented during the first 24 postoperative hours, 2 (J. N. and M. K.) died in the operating room, and 1 (M. F.) had a circulatory crisis which in itself could explain prolonged cerebral depression. All 22 other patients regained continuous electrical activity in less than 30 min. and experienced an uneventful recovery. We attach grave prognostic significance, therefore, to a delay of more than 30 min. in return of continuous electrocortical activity following restoration of circulation.

Another interesting relationship may be seen from the graph. The 30-minute ordinate intersects the regression line at the abscissa of 7½ min. (450 seconds) of circulatory arrest. This duration of occluded circulation compares closely with the safe time limit (8 min.) set by most surgeons from clinical experience. The observation that a series of 2 such episodes of circulatory arrest may be tolerated without undesirable electroencephalographic or clinical effects, if each arrest is separated by a recovery period long enough for the electroencephalographic pattern to return to the preocclusion level, is of clinical importance. This suggests that there is little reason to exceed 7½ to 8 successive min. of circulatory arrest in the occasional patient whose defect cannot be closed in this period of time, a series of two occlusions being tolerated better than one period of prolonged circulatory arrest of 12-min. duration.

The character of electroencephalographic patterns evolved once electrical activity returned was of prognostic significance. Patients who were subjected to arrested circulation of short duration and whose operative and postoperative course was uncomplicated invariably developed activity which rapidly progressed to patterns of relatively light cerebral depression.

On the other hand, patients subjected to prolonged circulatory arrest with complicated or

disasterous operative or postoperative course developed activity which did not progress rapidly to patterns of light cerebral depression. Indeed, their electroencephalographic patterns would frequently lapse into periods of prolonged silence after electrical activity was established.

If the electrical silence accompanying circulatory arrest results from accumulated metabolites, any procedure reducing metabolic rate should diminish the adverse effects of circulatory standstill. One might therefore reasonably suppose that electrocortical activity would return sooner after arrest at lower temperatures. Thus, the regression line previously discussed might either be displaced to the right, or the slope decreased during deeper hypothermia. To demonstrate such alterations, many observations at widely different temperatures and for varying durations of arrest are needed. We do not feel, therefore, that failure to demonstrate such alterations in the present study is of significance.

CONCLUSIONS

1. The electrocortical events following planned circulatory arrest during hypothermia are of prognostic significance. Favorable prognostic signs are the return of continuous electrocortical activity within 30 min. of restoring the circulation and the rapid progression of electroencephalographic patterns to levels of light cerebral depression once electrical activity returns. Unfavorable events are a delay of more than 30 min. in return of continuous activity, failure of patterns to rapidly progress into levels of mild cerebral depression, reappearance of prolonged periods of electrical silence, and presence of file type patterns following restoration of circulation.

2. Time lapse between restoration of circulation and onset of continuous electrical activity is a function of duration of circulatory arrest.

3. Two episodes of circulatory arrest, separated by a "rest period" during which circulation is restored and the electroencephalograph allowed to develop patterns of light cerebral depression, is tolerated better than a single episode of prolonged circulatory arrest.

4. Electroencephalographic evidence confirms the clinical impression that 7½ to 8 successive min. of circulatory arrest at hypothermic temperatures is safely tolerated.

SUMMARY

The electroencephalographic effect of occluded circulation during hypothermia in 28 human patients was investigated. Good correlation was found between duration of occluded circulation and the character of electrocortical activity developing after restoration of circulation. The time lapse between restoration of circulation and onset of continuous electroencephalographic activity as well as the type of electroencephalographic patterns developing after restoration of electrical activity were found to be of prognostic significance.

Dr. Verne L. Brechner
University of California Medical Center
Los Angeles 24, California

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SURGICAL TREATMENT OF THE OCCULT ISLET CELL TUMOR*

PIERCE J. FLYNN, M.D., AND LLOYD C. MCDONALD, M.D.

Los Angeles, California

The removal of an islet cell tumor of the pancreas is a dramatic and gratifying procedure. With a low operative mortality and morbidity, the patient is generally cured of a potentially fatal disease. Since Graham[5] reported the first surgical cure of organic hyperinsulinism in 1929, numerous reports have appeared in the literature confirming the amenable nature of this condition to surgery.

In some instances, however, the pancreatic tumor cannot be located despite an exhaustive search. The recommended procedure[1, 3] in this situation has been a resection of the body and tail of the pancreas. The results of such blind resections have not been satisfactory, since the tumor is found on pathologic examination in only a small percentage of cases. Porter and Frantz[8] have reviewed the experience of 52 patients with islet cell tumor at the Columbia Presbyterian Medical Center and have emphasized that hyperinsulinism is not relieved unless the tumor is removed. Although David and Campbell[3] reported good results in 23 of 36 blind distal pancreatectomies, in which the tumor was resected in only 5, there is reason to doubt the accuracy of the diagnosis and the adequacy of the follow-up.

CASE REPORTS

Since the opening of the U. C. L. A. Medical Center in 1955, the diagnosis of islet cell tumor of the pancreas has been confirmed at surgery in 5 cases. The tumor was located in the body or tail of the pancreas in 3 patients and was successfully treated by local excision. Two cases of islet cell tumor were cured by total pancreatectomy after the original exploration did not locate the tumor and distal pancreatectomy failed to control the symptoms of hyperinsulinism. In each case, subsequent resection of the head of the pancreas revealed a small buried tumor. In view of this experience and that of Porter and Frantz, a new approach to therapy is proposed when the surgeon is unable to locate the tumor on original exploration.

Case 1. J. B. (UCH, LA, 012-65-03), a 36-year-old Caucasian man, was first seen at the U. C. L. A. Medical Center on September 26, 1956, with complaints of increasingly severe hypoglycemic episodes of 1 year's duration. He had received psychiatric care during this time for these attacks. Prolonged fasting produced attacks of hypoglycemia with blood sugars of 35 mg. per cent. These attacks were relieved promptly with ingestion of carbohydrate. The preoperative diagnosis was pancreatic islet cell tumor, and laparotomy was advised. The patient was explored for the first time on October 5, 1956. At operation the entire body and tail of the pancreas were normal to inspection and palpation. The head of the pancreas and duodenum were mobilized and thorough palpation of the former failed to reveal any suspicious area. After a 2-hour exploration it was decided to perform a distal pancreatectomy; the body and tail were resected along with the spleen. Pathologic dissection of the resected specimen failed to demonstrate an islet cell tumor. Postoperatively, the patient continued to have hypoglycemic attacks identical to those before operation.

On October 23, 1956, a left subphrenic abscess was drained. During the patient's slow recovery from the latter infection his attacks continued despite a strict dietary regimen. He gained 50 pounds in the year following surgery, and finally his symptoms became so severe that re-exploration was recommended.

On November 19, 1957, he was explored for the second time. The head of the pancreas and the duodenum were again mobilized. Frozen sections were obtained from one suspicious area in the head, but only normal pancreatic tissue was revealed. Therefore, the head and uncinate process of the pancreas, along with the duodenum, were excised and a choledochojejunostomy and gastrojejunostomy were performed. On pathologic section of the specimen there was a 1-cm.-diameter nodule centrally situated deep within the head of the pancreas (fig. 1). This nodule proved to be an islet cell adenoma on microscopic examination.

Postoperatively the patient was dramatically

* From the Department of Surgery, University of California Medical Center, Los Angeles 24, California.

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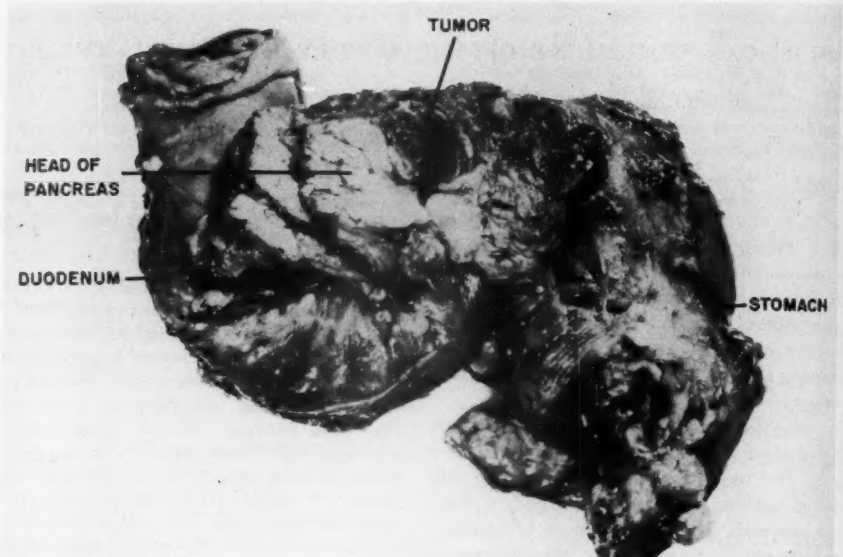

FIG. 1. Head of pancreas resected at second exploration. Sectioning of gland revealed a buried islet cell tumor 1 cm. in diameter.

relieved of his hypoglycemic attacks. He required varying doses of insulin and Viocase tablets. He remained essentially well until March 1959, when a transthoracic vagotomy was performed because of the development of a marginal ulcer. A revision of the gastroenterostomy was done March 1, 1959, because of partial stomal obstruction. When last seen in the Outpatient Clinic on March 18, 1959, he was asymptomatic and his weight has remained stable.

Case 2. S. C. (UCH, LA, 014-83-09), a 42-year-old Caucasian woman, was first seen by the medical service at the U. C. L. A. Medical Center on December 16, 1957, at which time she gave a history of 7 months of intermittent blackout spells. These episodes occurred several times a day and were always readily relieved by the ingestion of carbohydrate. Following a thorough study a diagnosis of functioning islet cell adenoma was established. Numerous blood sugar levels below 50 mg. per cent with associated periods of confusion and disorientation were noted. These were corrected immediately by administration of glucose.

After consultation with the endocrinology service, 200 μc. of radioactive zinc in saline and zinc chloride were given intravenously 10 days before surgery. It was hoped that the zinc, which is normally taken up by islet cell tissue, would be concentrated in a islet cell adenoma to a degree that would be detectable with a Geiger counter at operation.

The patient was explored for the first time on April 21, 1958. At operation the Geiger counter was carefully scanned over the pancreas, but no definite area of increased activity could be found. After careful palpation and inspection of the entire pancreas failed to demonstrate a tumor, one-third of the head and the entire body and tail of the organ were resected. On pathologic examination both gross and microscopic, no evidence of islet cell adenoma was found. Postoperatively the patient continued to have similar hypoglycemic attacks. Because of the severity of her symptoms she was re-explored on June 20, 1958. For the second time no tumor could be found. A resection of the remainder of the pancreas plus the duodenum and gall bladder was done. A choledochojejunostomy and gastrojejunostomy were performed. Dissection of the specimen revealed a 1-by 1.2-by 1.3-cm. nodule within the remainder of the head of the pancreas. Microscopically this proved to be an islet cell adenoma. Postoperatively the patient was completely free of hypoglycemic attacks. She has remained well and has been followed regularly in the Outpatient Clinic and has required between 70 and 80 units of NPH insulin plus 10 to 16 Viocase tablets per day. She was last seen on March 13, 1959, 11 months postoperatively and is well.

DISCUSSION

The clinical aspects of hyperinsulinism (*i.e.*, functioning islet cell tumor) are well known.

Since the bizarre manifestations of hypoglycemia may simulate other disorders, an erroneous diagnosis is frequently made initially. Once the diagnosis of spontaneous hypoglycemia is established, it is necessary to distinguish between functional hyperinsulinism, organic hyperinsulinism, or hepatogenic hypoglycemia as the cause. Conn and Seltzer[2] have recently provided a complete etiologic classification of spontaneous hypoglycemia and the important differential diagnostic criteria. The characteristic syndrome of a functioning islet cell tumor is a state of hypoglycemia brought on by fasting with the blood sugar findings below the 50 mg. per cent level and immediate relief following the ingestion of glucose (Whipple's triad). It is extremely important that the preoperative work-up be thorough before undertaking surgery.

The pancreas may be adequately explored by utilizing a transverse incision in the epigastrium. Division of the gastrocolic ligament widely offers good exposure to the body and tail of the pancreas. Reasonably accurate bimanual palpation of the body and tail can be obtained by gently dissecting free the small veins and peritoneal reflections along the inferior and superior border of the pancreas. It is extremely important to "mobilize" the pancreas fully so that careful, detailed palpation of the anterior and posterior surfaces of the gland can be accomplished. It is believed that by closely examining the distal pancreas in such a manner, most of the tumors in this portion of the pancreas will be detected. A factor which aids in this detection is the established finding that a great majority of the islet cell tumors in the body and tail of the pancreas are superficially located in contrast to the usual deep position of the tumors in the head.[4]

The head of the pancreas may be examined bimanually by incising the peritoneum along the lateral border of the duodenum and reflecting the duodenum medially. Tumors nestled in the thicker, more bulbous position of the head are much more likely to escape detection, although meticulous dissection and palpation will frequently be rewarding in locating a tumor.

Once the tumor is located, simple excision or enucleation may be carried out. Since 1 out of 10 cases will have multiple functioning tumors, a search for additional tumors is mandatory. Ectopic tumors are rare and are usually located close to the pancreas. Exclusive of the operative mortalities, the cure rate following removal of localized tumors has been reported by Breidahl and associates[1] as 93 per cent in a group of 42 well followed cases, and as 87 per cent by Howard and associates[6] in a collected group of 200 cases.

In a disturbingly high percentage of explorations for islet cell tumor the surgeon is unable to find the lesion. The frequency of negative explorations varies according to the experience of the operator, but from the accumulated reports it appears that 1 out of 4 explorations will fail to demonstrate the tumor. In such a situation the recommended procedure has been to perform a resection of the distal pancreas, removing all of the gland to the left of the superior mesenteric vessels. The proposed rationale for this procedure is based on several points: (1) 70 per cent of the islet cell tumors found at surgery are located in the body and tail of the pancreas and (2) massive resection of normal or hyperplastic pancreatic tissue will decrease the supply of insulin, in the event no tumor is found in the resected specimen.

There is reason to doubt the validity of distal pancreatectomy on the basis of these arguments. Since it is mainly from operative findings that the statistics of tumor location are obtained, it is true that the vast majority of "palpable" tumors are in the distal pancreas. However, it is quite likely that the actual incidence of functioning tumors involving the head of the pancreas is considerably higher.[7] It is our belief that if the tumor cannot be located after a thorough and painstaking exploration of the entire gland, it is buried in the head of the pancreas. In 1950 Howard and associates[6] collected 77 cases from the literature in which a "subtotal" pancreatic resection was performed when the surgeon was unable to find the tumor. Histologic examination of the resected specimen revealed an islet cell tumor in 12 cases or 15 per cent of the resected group. The remaining cases had histologic diagnoses of hyperplasia of islet cells, hypertrophy of islet cells, chronic pancreatitis, hamartoma, and normal pancreas. Of the 65 patients in which a tumor was not found by the pathologist, 26 (40 per cent) were reported as "cured."

This favorable "cure" rate following distal pancreatectomy without removing the tumor has not been the experience in this institution or that of others in recent reports. Breidahl and associates[1] reported from the Mayo Clinic in 1955 that 12 of 15 cases in which normal pancreas was discovered following a partial pancreatectomy continued to have symptoms of hyperinsulinism. Porter and Frantz[8] in 1956 have had to re-explore every patient because of persistence or recurrence

of symptoms, if at the original operation no tumor was found in the resected specimen. Resection of distal pancreas with hyperplasia of the islet cells as the sole pathology has been reported as relieving symptoms of hypoglycemia. Although hyperplasia of the islet cells may be a cause of hyperinsulinism, we tend to agree, along with Warren and Le Compte,[9] Breidahl and coworkers, and Porter and Frantz that no convincing evidence has thus far been presented to support this theory and that prolonged follow-up on these cases will reduce the number of "cures."

If the preoperative work-up has been thorough and the diagnosis of hyperinsulinism reasonably certain, exploratory laparotomy is indicated. Excision of a localized tumor presents no unusual problem. If the tumor cannot be located after the pancreas and ectopic sites have been thoroughly explored, and the operator feels confident that the gland contains no visible or palpable tumor, we propose that resection of the head of the pancreas be considered as the initial procedure. We feel that a high percentage of the tumors will be embedded in this portion of the pancreas when careful exploration fails to reveal the tumor grossly. With clinical experience indicating that these patients are not cured of hyperinsulinism unless the tumor is removed, an increasing number of cases will require a total pancreatectomy after an original distal pancreatectomy has proved unsuccessful. The serious and disabling nutritional consequences of total pancreatectomy and the additive mortality and morbidity of repeated abdominal explorations may be significantly lessened by electing to resect the head of the pancreas in such circumstances at the original exploration. It is recognized that the resection of the head of the pancreas carries a higher operative mortality and morbidity than resection of the body and tail, but we also feel that the functioning tumor will be removed in a great majority of cases, and the distal pancreas will be left intact for endocrine and exocrine function.

The utilization of radioactive zinc in an effort to localize the functioning islet cell tumor is being given further clinical trial. The ultimate answer to the problem of accurate localization of the occult islet cell tumor probably lies in the field of radioactive isotopes.

SUMMARY

The syndrome of hyperinsulinism is briefly summarized. In 25 to 30 per cent of surgical explorations for islet cell tumor the surgeon is unable to locate the lesion. The recommended procedure in these instances has been a blind distal pancreatectomy. In approximately 15 per cent of these blind resections the tumor is removed. The clinical results of the cases in which no tumor was found on the resected specimens have been unsatisfactory. It is proposed that the great majority of these occult tumors are embedded in the head of the pancreas. It is suggested that resection of the head of the pancreas be performed at the time of the initial negative exploration.

Two cases are presented in which distal pancreatectomy failed to relieve the symptoms of hyperinsulinism and subsequent total pancreatectomy resulted in locating the tumor and cure of the patient.

Dr. Pierce J. Flynn
University of California Medical Center
Los Angeles 24, California

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CORRECTION OF GLUTEUS MEDIUS GAIT: DYNAMIC BALANCE GAIT*

CHARLES O. BECHTOL, M.D.

Los Angeles, California

The abductor muscles of the hip hold the torso erect during the time the body weight is borne on one leg during walking. This action of the abductor muscles is necessary because the center or rotation of the hip joint is placed lateral to the center of gravity of the body. Inman[2] has shown that the abductor muscles must supply a force of about 1½ times the body weight, and this results in a total force through the hip joint of about 2½ times the body weight. The hip abductor mechanism may fail, either through weakness or paralysis of the muscles, or through lack of an effective lever arm of the femur in high thigh amputations (fig. 1). The abductor mechanism may also be thrown out of action in the so-called antalgic gait described by Calve and associates.[1] In the antalgic gait elimination of the force of the abductor muscles reduces the force transmitted through the painful hip joint.

ABDUCTOR LIMP

In each of these gaits the torso is shifted over the affected hip. This results in a shifting of the center of gravity of the body near to the center of rotation of the hip joint, thus eliminating any need of action of the abductor muscles, and at the same time reducing the force transmitted through the hip joint. This method of balancing the torso over the hip joint is effective, whether the patient is standing (static) or walking (dynamic). The balance, however, is achieved at the expense of a marked lateral bending of the spine and with an obviously abnormal gait. This excessive bending of the spine can be avoided by the dynamic method of balance. Because this method is dynamic, however, it is effective only when the subject is walking and not while standing still.

DYNAMIC BALANCE GAIT

The dynamic balance gait substitutes the inertia of the torso as it sways toward the weight-bearing hip for the shift of center of gravity which is accomplished by bending the torso. The normal side-to-side displacement of the body during walking is increased (fig. 2). Even when walking at the slow cadence of 60 steps per minute, weight is born on each leg for only 1 second. This, then, allows ½ second for deceleration of the body as it swings toward the affected hip and another ½ second for acceleration of the body as it begins to fall away from the affected hip. Balance can easily be maintained for these short periods of time and becomes even easier at a more rapid cadence. The dynamic balance gait thus achieved, does not require any lateral bending of the spine and considerably reduces the tendency toward back pain, frequently associated with the gluteus medius gait. The dynamic balance gait also approaches the normal, cosmetically, and may not be noticed by the untrained observer (*cf.* fig. 3).

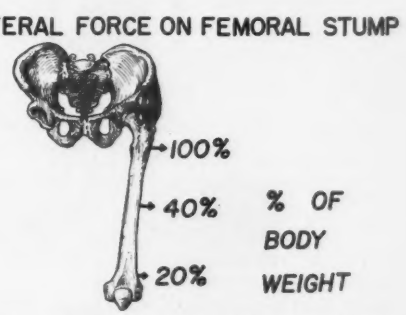

FIG. 1. The force exerted by the hip abductors is about 150 per cent of body weight. The lateral pressure against the socket wall depends upon the length of the femur stump. The high lateral pressures in short stumps are painful and prevent the amputee from effectively using his hip abductor mechanism.

TEACHING DYNAMIC BALANCE GAIT

When the subject first learns to walk with paralyzed hip abductors, a painful hip, or a short, above-knee amputation the position which seems to him to be the most stable is that with

* From the Department of Surgery, Division of Orthopedic Surgery, University of California Medical Center, Los Angeles, California.

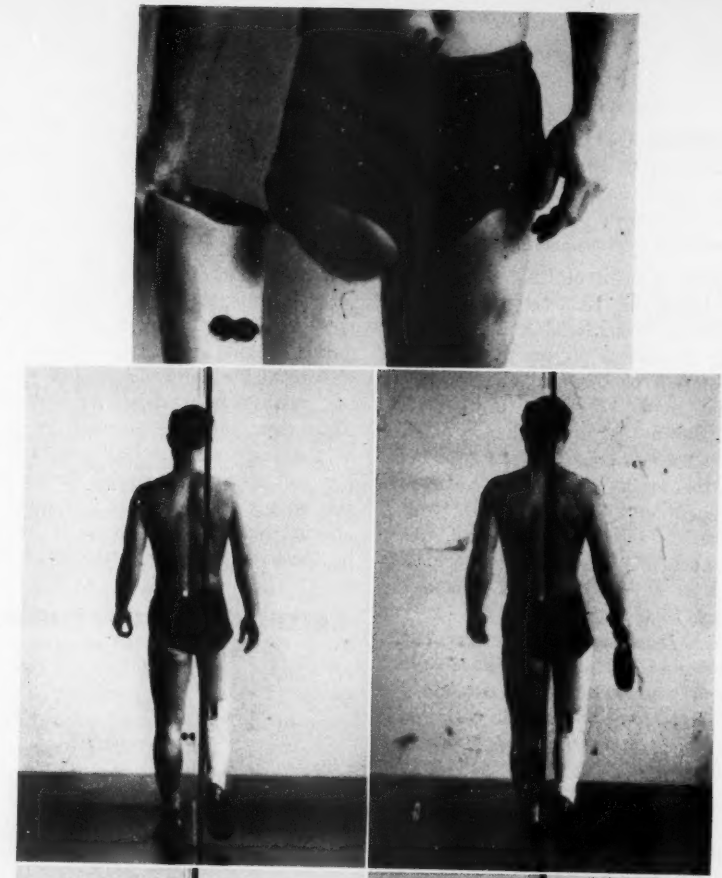

FIG. 2. On the left (without weights) the subject shows lateral sway of his torso and wide spacing of his feet. A 20-pound weight in his right hand shifts the center of gravity toward the amputation, and reduces torso sway and wide foot spacing. While carrying the weights, his gait approaches normal. The normal leg can easily cope with this shift of the center of gravity, because of its reserve power. Photographs are enlarged from 16-mm. motion pictures. Inset shows very short stump.

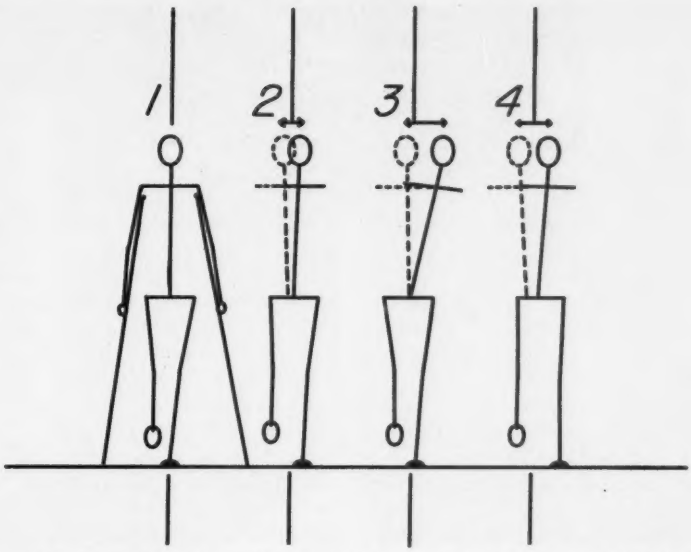

FIG. 3. In crutch walking (*1*), side-to-side sway is eliminated, since the foot is placed directly beneath the center of gravity of the body and the crutches give equal support from each side. In normal walking (*2*), there is moderate side-to-side displacement, and the feet are not placed directly under the center of gravity of the body. In the gluteus medius gait (*3*), the torso is shifted over the weight-bearing hip to shift the center of gravity nearer the center of rotation of that hip. This is accomplished by lateral bending of the spine and a cosmetically awkward gait. The dynamic balance gait (*4*), exaggerated the lateral shift of the body seen in normal walking and eliminates the necessity of bending the spine to shift the center of gravity over the weight-bearing hip.

his torso shifted over the affected hip. At this time he is interested only in gaining a position which seems to give him the least fear of falling and has little regard for the cosmetic results or the eventual chronic strain on his back. Only those subjects who have a superior sense of balance will spontaneously learn the dynamic balance gait. Subjects who can walk either method state that in walking with the "gluteus medius" gait, they feel as though they were shifting their pelvis away from the weight-bearing hip, but when walking with the dynamic balance gait, they feel as though they were shifting their pelvis toward the weight-bearing hip. Instructions given to a subject learning the dynamic balance gait are therefore as follows: (1) to walk with the feet spaced slightly wider apart; (2) to increase the lateral shift of the entire body; and (3) to shift the pelvis toward the weight-bearing hip when weight is born on the affected side.

SUMMARY

1. In the gluteus medius weakness gait, antalgic gait, or short thigh amputation, a shift of the center of gravity over the affected hip is commonly employed to balance the torso or to reduce pain in the hip.

2. The dynamic balance gait substitutes the inertia of the body resulting from increase of the normal lateral displacement for the shift of the center of gravity. This method is effective only in walking (dynamic) and not in standing (static).

3. The dynamic balance gait reduces lateral spine bending and pain, and is cosmetically much more superior.

University of California Medical Center
Los Angeles 24, California

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TRACHEAL STRETCHING AND METAPLASIA OF THE TRACHEAL RINGS FROM CARTILAGE TO BONE FOLLOWING THE USE OF AORTIC HOMOGRAFTS*

JOEL J. PRESSMAN, M.D., AND MILDRED BURTZ SIMON

Los Angeles, California

Reconstruction of the cervical trachea is a vastly different problem from that of thoracic trachea, the former enjoying several advantages. The trachea in the neck is more easily accessible, it can be temporarily bypassed by the use of tracheotomies, and lies in a good muscle bed which provides a rich blood supply.

This study represents fundamental research involving the use of more than 200 dogs, the experiments having been originally planned to study the possibility of repair of the cervical trachea and esophagus by a variety of materials. These include tubes made of plastic sponge, nylon and Dacron mesh, inert metallic mesh, calcified and decalcified long hollow bones rasped out to create a lumen, and decalcified scapula as a "wrap-around." Of these latter two, some were chromicized to delay absorption and some were not. In some experiments the implants were inserted at the time of the initial surgery, and in others, after a delay, to permit the formation of a fibrous tube after which the materials were inserted as wrap-arounds in a second stage procedure, hoping for their incorporation as "stiffeners" in the previously formed tube.

Earliest attempts consisted of the use of indwelling polyethylene tubes which bridged the gap of full lumen defects or in other experiments of wide fenestra (6 by 2 cm.) leaving the membranous trachea intact. A cover of various materials including aorta was used over the tube to seal the fenestra in the trachea. The membranous tube that formed about the insert, although well formed, was always flaccid and in no attempt did it serve as an adequate airway, invariably collapsing with inspiration. When the polyethylene insert was permitted to remain, it frequently became occluded by granulomas at the ends of the tube.

After 3 years, 1 dog surviving the implantation of a polyethylene tube presented a most interesting finding. Leukoplakia-like deposits occurred on the mucosal surface of both the larynx and the trachea above and below at the site of the implant as well as the original site, probably due to movement of the tube. These, microscopically, are hyperkeratotic, greatly thickened layers of epithelium presenting evidence of histologic activity. Based upon experiences with humans they need to be considered premalignant. There are no previous reports of leukoplakia having been experimentally produced anywhere in the body, for which reason the observation is of especial interest.

USE OF AORTIC HOMOGRAFTS

The aorta has of course been used successfully to replace segments excised from diseased blood vessels. Occasional attempts have been made to utilize it for the repair of other organs, but reports upon the subject are meager.

Attempts herein reported consisted of resecting segments of cervical trachea measuring 6 by 2 cm. which constituted essentially all the cartilagenous rings over a 10-ring length and essentially that segment of the circumference represented by the cartilagenous rings. A full lumen polyethylene tube was inserted as a bridge and a homologous lyophilized aortic patch sutured over the defect. Stainless steel fixation wires were passed through-and-through using a large hypodermic needle as a trochar through which the wire was passed.

During the course of current experiments to observe the utility and fate of such homologous aortic tissue transplanted into the neck as an adjunct to the repair of excised segments of cervical trachea, several interesting phenomena have come to light. These are: (1) the long period of time over which aorta may retain its gross and histologic identity; (2) the phenomenon of tracheal stretching by which the contraction and shrinking of the aortic segment actually elongates

* From the Department of Surgery, Division of Head and Neck Surgery, University of California School of Medicine, Los Angeles 24, California.

FIG. 1.*A*, polyethylene tube and rehydrated aortic homograft sutured *in situ* demonstrating wire fixation sutures. *B*, aortic homograft after 9 months.

FIG. 2. Internal aspect of trachea split posteriorly demonstrating narrowing of tracheal fenestra and epithelialization of aortic transplant.

the remaining trachea; and (3) the very exciting phenomenon of the conversion of adjacent tracheal cartilagenous rings to actual true bone.

The aorta used in dog experiments is from donor dogs. It is dehydrated and sterilized in the Bivac lyophilizer.

FATE OF AORTA

A great difference exists in the survival time of aortic homografts placed in the trachea to cover large window defects and those used to replace the cervical esophagus. In the latter all evidences of aortic implants disappear within a period of months, but in the instance of aortic implants into the cervical trachea, although a great deal of fibrosis and contraction takes place, the presence of aortic tissue in large patches (6 by 2 cm.) is, even in the gross, clearly identifiable after periods as long as 3 years. It becomes firmly adherent to the surrounding structures, both fibrous and cartilagenous, and blends intimately with them (fig. 1, *A* and *B*).

In figure 1*B* with the trachea split posteriorly, the interior of the aortic implant can be identified and is seen to be covered with normal respiratory epithelium. Healing of the largest possible fenestrae is therefore complete including epithelialization. Of particular practical value is the fact that in almost no instance has there been evidence of the formation of occluding granulomas as is almost invariably the case when a polyethylene tube is used as a bridge without an aortic cover.

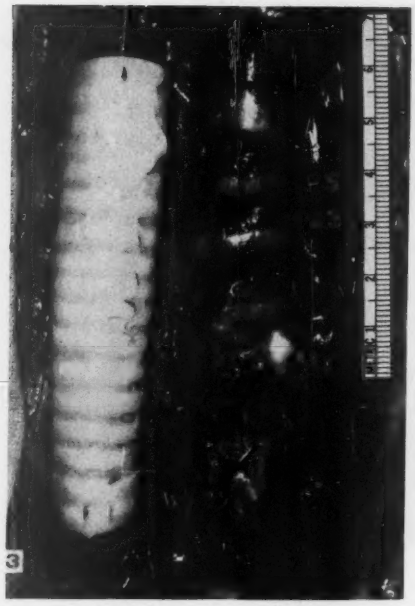

FIG. 3. Stretching of membranous trachea between rings from fibrosis of aortic implant. Normal trachea (*right*) for comparison (3 years postoperative). (From Pressman, J. J., and Simon, M. B. Observations upon experimental repair of the trachea. Surg. Gynec. & Obst., *106:* 58, 1958.)

The aortic covered window appears very much narrower and shorter than when first created, due to shrinkage and contracture of the graft. The implanted aorta retains much of its identity not only in the gross, but microscopically, for long periods of time, the elastic fibers retaining their normal appearance and pattern for as long as 3 years, representing the limit of the experiments. The retention of various elements of the aortic structure is variable, the elastic tissue structure surviving long after other elements have disappeared. Intimate blending occurs between the elastic tissue elements of the aortic implant and the adjacent tracheal rings and perichondrium. The elastic tissue of the media obviously survives as such for long periods of time, and it is the presence of this element which differentiates the aorta from other structures used as implants. To it the aorta owes its value as a transplant in the replacement of other vessels, and for the repair of the cervical trachea and esophagus as well.

TRACHEAL STRETCHING

The second phenomenon considered to be of unusual interest is that of tracheal stretching. This takes place when the full lumen of the trachea is replaced by an equally long segment of full lumen of aorta. The stretching results from fibrosis of the aorta with its subsequent contraction. It is probable that fibrosis with contraction and stretching of residual trachea would occur in any fibrous tube joining the severed ends, but the process has not been observed or reported elsewhere.

The inevitable process of contraction which takes place in all newly formed fibrous tissue, exerts its relentless pull upon the tracheal segments above and below the defect. This pull stretches the trachea by widening the membranes between the tracheal rings. In fig. 3, a normal trachea has been superimposed for purposes of comparison. On the right is the experimental trachea demonstrated 3 years postoperatively following resection of a length of 6 cm. or 10 rings long, and the insertion of a corresponding length of aortic bridge. The degree of stretching of the trachea can be easily observed, and may be compared with the appearance of the normal trachea particularly insofar as the width of the membranous spaces between the rings is concerned. It is quantitatively such that in one area two cartilagenous rings and the intervening membranes of the stretched segment occupy the length of 8 normal rings together with their membranous interspaces. The stretched tracheal segments have literally been pulled up out of the thorax by the stretching process, and the adjacent rings, although not evident in the photograph, are distorted in shape particularly in cross-section as previously reported.

METAPLASIA OF CARTILAGENOUS RINGS TO BONE

The third phenomenon, the most striking of all, takes place in the tracheal rings adjacent to the aortic implant. This is the actual metaplasia from cartilage to pure bone, including the presence of osteoblasts and what appears to be a true haversian system. The transition is a gradual one from normal cartilage through various stages of calcification to that of the formation of cancellous bone.

FIG. 4. Microscopic cross section of the normal cartilagenous ring
FIG. 5. Microscopic cross section 1 year after aortic implant demonstrating absorption of cartilage and deposits of calcium.

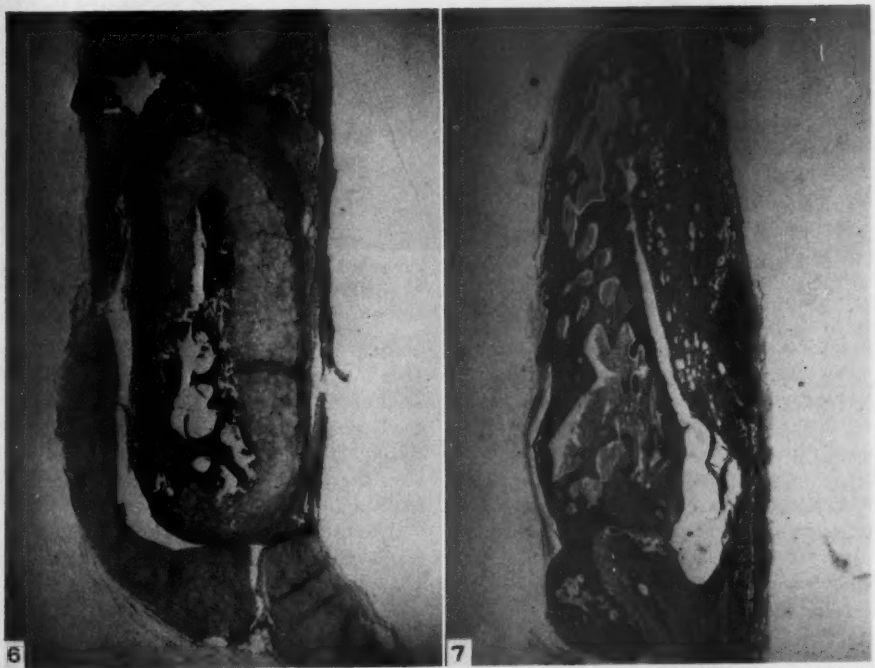

FIG. 6. Microscopic cross section after 2 years demonstrating process of decalcification and the beginnings of true bony trabeculae. Elastic tissue can be seen on the right and below.
FIG. 7. Microscopic cross section after 3 years shows the tracheal ring no longer recognizable as cartilage; it appears to be true trabecular bone with osteoblastic activity and osseous proliferation.

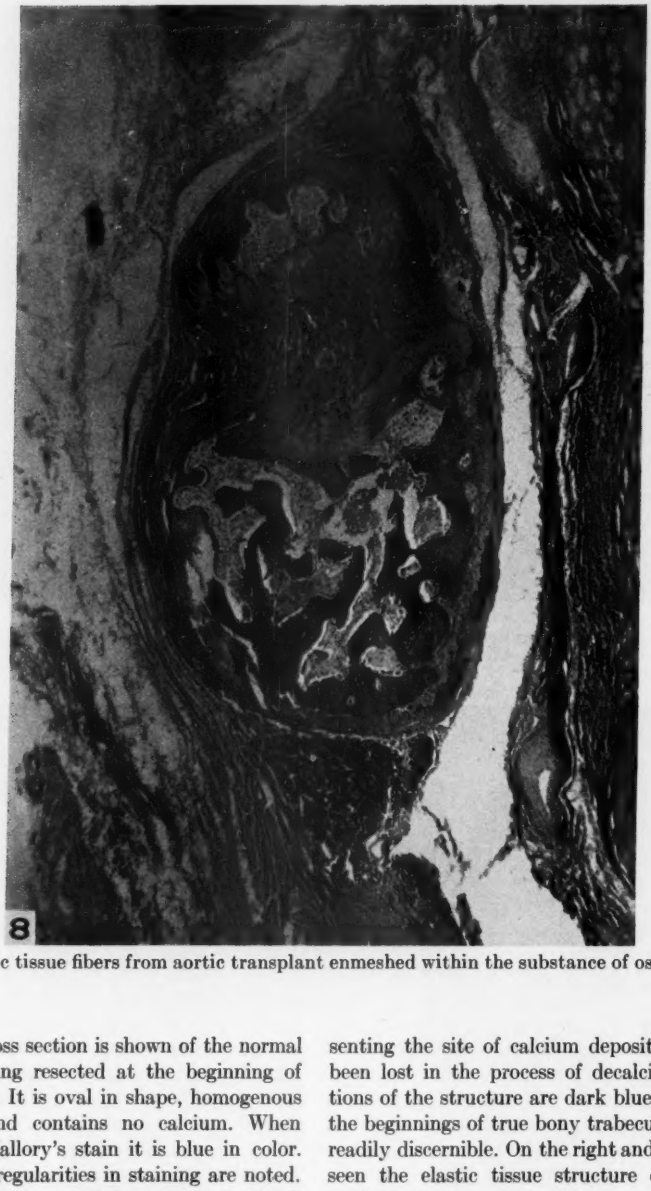

FIG. 8. Elastic tissue fibers from aortic transplant enmeshed within the substance of ossified tracheal ring.

In fig. 4 a cross section is shown of the normal cartilagenous ring resected at the beginning of the experiment. It is oval in shape, homogenous in structure and contains no calcium. When stained with Mallory's stain it is blue in color. After 1 year, irregularities in staining are noted. The cartilage has a mottled appearance. Small defects are seen representing sites of absorption of previous cartilage. Yellowish flecks with Mallory's stain are present, these being deposits of calcium (fig. 5).

At 2 years, as demonstrated in fig. 6, the cartilage stains very pale with vacuoles representing the site of calcium deposits which have been lost in the process of decalcification. Portions of the structure are dark blue, representing the beginnings of true bony trabeculae which are readily discernible. On the right and below can be seen the elastic tissue structure of the aortic implant after 2 years *in situ*.

After 3 years, as seen in figure 7, the tracheal ring is no longer oval but is distorted in shape, becoming irregular and elongated on cross section. This represents distortion from the stretching process. It is no longer recognizable as cartilage but has the appearance of true trabecular

FIG. 9. End vessels to tracheal rings apparently entering the membranous septa and supplying only the ring above and ring below.

bone with osteoblastic activity and osseous proliferation. Some residual of the preliminary stage of calcification is evidenced by the yellow staining areas. This apparently is a true metamorphosis from cartilage to bone dependent upon the experiment described, since no deviation from the normal histology took place in areas of the trachea sufficiently distant as to be unaffected by the stretching process. Ordinarily, true bone formation does not take place in the tracheal rings, although, of course, calcification is common in the aging process. It well may be that this experimental production of bone in the tracheal rings is unique, not having been reported experimentally under other circumstances.

After 3 years the transition from cartilage to bone is complete. By this time there is no residual cartilage or evidence of preliminary calcification. Bone with the classical formation of trabeculae entirely replaces the cartilagenous structure of the tracheal ring (fig. 7).

One additional phenomenon is of peculiar interest, but no particular significance can be attached to it at this time, nor can the phenomenon be explained. The elastic tissue fibers of the aortic transplant in figure 8 are still clearly recognizable after 3 years. In the upper third of the ring these elastic tissue fibers have extended from the periphery of the tracheal ring into its substance replacing the bony elements in that particular area. The nature of the inclusion of these inert elastic fibers within the bone and their persistence after 3 years is of especial interest but, has not been demonstrable in any other specimen.

Reasons for the transition of cartilage to bone are not entirely clear. The metaplasia does, however, occur only when the stretching phenomenon takes place, but its beginnings in the form of calcium deposits are seen before any visible stretching. It is nevertheless believed to result from anoxia based upon the peculiarities of the blood supply of the tracheal rings. This is from a series of transverse vessels here demonstrated (fig. 9) which pass from a main trunk to the membranous interspaces supplying only the ring above and the ring below. As the membrane housing the vessel is stretched and thinned, the vascular supply seems to become gradually occluded. The avascular appearance of the membranous rings is obvious in all specimens. This lessening of the vascular supply to the rings possibly accounts for the transition from cartilage to true bone. It is very likely a reaction to injury as is seen in the cartilages of the joints of the skeleton, but this is pure conjecture and the basic factors involved are actually unknown.

SUMMARY

From the practical standpoint, no homograft created from any other structure or any artificial implant has been found to be of equal value to the use of aorta in the repair of large tracheal defects. By rapidly blending with surrounding structures, it prevents the formation of occluding granulomas and by contraction promotes the closure of large defects of the cervical trachea. Its use has furthermore provided a means of studying the controlled metaplasia of cartilage to bone, a phenomenon which experimentally has not previously been reported. Experiments in which large tracheal defects have been closed with aortic homografts have provided examples of the phenomenon of tracheal stretching which offer opportunities for the successful repair of tracheal defects previously not considered amenable to repair without the insertion of artificial prosthesis.

Dr. Joel J. Pressman
University of California School of Medicine
Los Angeles 24, California

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THE EFFECT OF THE LIVER ON SECRETIN*

JAMES C. HART, M.D.,† AND JAMES S. CLARKE, M.D.‡

Los Angeles, California

The liver is anatomically located so that all substances which are liberated from the various organs of the portal bed must pass through it. It may, therefore, metabolize or excrete them, or allow them to pass unchanged. The operation of portacaval shunt furnishes a stimulus for us to increase our understanding of the role of the liver in modifying materials presented to it in the portal blood. At the same time it constitutes a tool for studying this problem.

Myriad chemical substances enter the portal blood from the abdominal viscera. Many of these, such as glucose, amino acids and ammonia, are known to be significantly metabolized in the liver.[4] With regard to hormones of portal bed origin, however, there has been little interest in ascertaining the importance of the liver in their metabolism. Grossman[2] made no mention of the role of the liver in their inactivation or of the effect of portacaval shunt on their action. Still[6] made no mention of the destruction of secretin in the liver.

It thus remains to delineate the function of the liver in metabolizing a number of hormones and chemical substances which rise in the portal bed and must traverse the liver before entering the general circulation. If the liver destroys them to a significant degree, their peripheral effect should be profoundly reduced because of the liver's interposition between their sites of origin and action; and if portacaval shunt is made, their action should be augmented above normal levels.

The present study was designed to determine whether the liver is more important than other body organs in the inactivation of secretin.

* From the Surgical Service, Veterans Administration Center, and the Department of Surgery, University of California Medical Center, Los Angeles, California.

† Resident in Surgery, Veterans Administration Center.

‡ Chief, Surgical Service, Veterans Administration Center, and Assistant Professor in Residence, Department of Surgery, University of California Medical Center.

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METHODS

Six mongrel dogs with weights ranging from 7.7 to 25.0 kg. were fasted for 20 hours and anesthetized with intravenous pentobarbital sodium. Through a midline abdominal incision the major pancreatic duct was isolated near its entrance into the duodenum. The duct was opened transversely, its duodenal end was tied, and its pancreatic cut end was cannulated for 0.5 to 1 cm. with a no. 18 or no. 15 polyethylene catheter tied in place by a single silk suture. The catheter was 10 to 15 cm. long and its distal end was placed in a calibrated centrifuge tube at the level of the abdominal wound for purposes of collecting the pancreatic secretion. A second polyethylene catheter was placed in one femoral vein and kept open with a slow infusion of physiologic saline solution. A third catheter was placed in a branch of the splenic vein.

Basal pancreatic secretion was collected for ½ hour. Then secretin* was given via the systemic (femoral vein) and intraportal (splenic vein) route and ½-hour collections of pancreatic juice made for each. The same dose of secretin, ranging from 1 to 10 clinical units (1 clinical unit equals 1 Ivy dog unit), was used for each pair of injections. The size of the dose and the route of injection were varied. The dose sizes were administered in the order shown in table 1, column 3. For any dose level and dog, the order of route of secretin injection appeared to have no effect on the volume of pancreatic juice secreted in response to it.

The volume of pancreatic juice secreted each ½ hour in the basal state and in response to secretin by each route was measured by inspection of the calibrated collecting tube.

RESULTS

The results are given in table 1. In all cases the pancreatic juice was clear and colorless. The basal secretion ranged from 0.1 to 0.2 ml. in ½ hour.

* We are grateful to James B. Hammond, M.D., of Eli Lilly and Company for furnishing us with ampules of secretin for experimental use.

TABLE 1

Volume of pancreatic juice secreted ½ hour after injection of secretin into femoral vein and splenic vein

$t = -0.800$; degrees of freedom = 16.

Mean difference of −0.14 is not significant at $P = 0.4$ level.[5]

Dog No.	Weight	Secretin Given*	Volume of Juice Secreted	
			Secretin given into femoral vein	Secretin given into splenic vein
	kg.	*units*	*ml.*	*ml.*
1	50.5	50	6.4	8.1
2	7.7	2.5	2.9	3.2
		1	1.5	1.65
3	14.6	5	3.95	4.65
		3	3.35	4.30
		1	0.95	1.1
		7.5	6.4	7.0
4	22.3	10	8.85	8.0
		1	0.95	0.75
		8	7.05	6.55
		3	1.95	1.65
5	25	4	4.45	3.7
		2	2.55	3.3
		5	5.55	4.9
6	15.9	5	6.7	7.4
		2.5	4.15	4.15
		1	1.4	1.0
Total			69.05	71.40
Mean average			4.06	4.20

* Units given in the order they were given to each dog.

After injection of secretin there was a rapid flow of juice which returned to basal levels within 15 minutes. The volume of pancreatic juice secreted increased with increasing doses of secretin. The volume of juice secreted was nearly the same for any given dog and dosage level regardless of whether the secretin was given into the femoral or splenic vein. The mean average volume of pancreatic juice secreted was 4.06 ml. in response to 17 injections of secretin by the femoral vein route. The mean average was 4.20 ml. in response to 17 injections in identical dosage by the splenic vein route. This difference is not significant. In fact, the reproducibility of the volume secreted in response to repeated identical doses of secretin, regardless of route of administration, was most striking.

DISCUSSION

Gerez and Weiss[1] reviewed several articles dealing with the effect of the liver on gastrointestinal hormones. They found that experimental evidence was conflicting and opinion divided as to whether the liver destroys secretin. Probably the divergence in findings was due to difference in the secretin preparations available; some of which owed their activity to histamine and other vasodilatins rather than to potent, specific secretin extractable from gastrointestinal mucosa and entirely free of vasodilatin.[2] We have found no papers since those discussed by Gerez and Weiss on the role of the liver in the metabolism of secretin.

Our findings are clear. The activity of the secretin in the blood supplying the pancreas, as measured by its stimulatory effect on flow of pancreatic juice, is the same whether the secretin is injected into the portal vein or into the peripheral vein. It follows that the liver has no special role in the inactivation of secretin, although it may participate in secretin metabolism to a degree comparable with other body tissues. If it were especially active in secretin destruction, intraportally injected secretin would be reduced in potency before entering the general circulation via the hepatic veins. Such is not the case.

As relatively pure preparations of other gastrointestinal hormones become available it will be of interest to see whether the liver plays an important part in their inactivation. Potent preparations of pancreozymin and cholecystokinin are at hand.[3] Although many gastrointestinal hormones appear to be polypeptides, there is no *a priori* reason why all should be treated similarly in the liver. Hence each must be tested. It seems likely that serotonin is broken down to a large extent in the liver, since the liver is rich in amino oxidase and the endocrine picture caused by carcinoid tumors is only seen when a considerable amount of tumor tissue is drained by extraportal veins.[7] This hypothesis concerning the importance of the liver in inactivation of serotonin requires experimental verification, using similar methods to those applied here to secretin.

SUMMARY

1. The volume of pancreatic juice secreted in response to an intravenous dose of secretin is the

same, regardless of whether the secretin is given into the peripheral or portal venous system.

2. Hence the liver has no more important role than other body tissues in the inactivation of secretin.

Dr. James C. Hart
University of California Medical Center
Los Angeles 24, California

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THYROID SURGERY AT THE U. C. L. A. MEDICAL CENTER

WILLIAM F. POLLOCK, M.D., AND DAVID H. SPRONG, JR., M.D.

Los Angeles, California

In the 3 years since the teaching hospital at the U. C. L. A. Medical Center opened, a total of 113 thyroid operations has been performed. The changing patterns in the current therapy of thyroid disorders are reflected in this experience.[5]

Before World War II the generally accepted treatment of Graves' disease was subtotal thyroidectomy after suitable preparation with iodine and various antithyroid drugs or sedatives. This method of therapy had a long history of proved efficacy. With the advent of effective antithyroid drugs of the thiourea series a brief period of "pure" medical therapy of Graves' disease was undertaken in some teaching centers. It is apparent now that this form of medical therapy does not yield enough long term remissions. Antithyroid drugs are a valuable aid in the preparation of the severely toxic patient for surgery, and they may offer a therapeutic-diagnostic "test" in the problem case, but as the sole definitive therapy they have not fulfilled their early promise.

The incidental discoveries which resulted from the studies in nuclear physics during World War II gave the medical profession a valuable tool for the study of thyroid disorders. The early work with iodine isotopes of very short half life was soon followed by the adoption of the longer lived isotope, I^{131}. The many advances in nuclear medicine have received added attention at the U. C. L. A. Medical Center because of the presence on this campus of a large project of the Atomic Energy Commission.

Radioactive iodine has altered the pattern of management of thyroid disorders markedly in this and other centers with similar equipment. It has become almost standard practice here for patients with thyroid disease to have radioiodine uptake studies in preference to determinations of the B.M.R. (basal metabolic rate). In many metabolic clinics the use of the B. M. R. has become almost a rarity. Various tests of organic blood iodine levels are also part of the diagnostic armamentarium.

From the surgeon's viewpoint the most important advance from the use of radioiodine has been the development of the "scanning" scintigram. It has become increasingly evident that this technique is very valuable in studying nodular goiters.

These changes in diagnostic methods have been accompanied by changing patterns of therapy. In the 3-year experience at this hospital only 3 patients have come to subtotal thyroidectomy for toxic diffuse goiter. One of these represented a failure of radioiodine therapy. Three others have come to surgery for the treatment of toxic nodular goiters. The vast majority of patients with hyperthyroidism are being treated with radioactive iodine.

This method applied to the diffuse goiter of classic Graves' disease might be considered the treatment of choice by some. The application of radioiodine therapy to toxic nodular goiters rests on much less secure ground, but has been the most common method of treatment at this institution. The hazards inherent in the application of radioiodine therapy to a hyperplastic gland engender some genuine concern.

The administration of therapeutic amounts of radioactive iodine to hyperthyroid patients is equivalent to administering 7000 roentgens of x-ray therapy to the neck. Paradoxically, smaller doses of radiation seem to be more carcinogenic than the larger doses. It is generally agreed that this amount of radiation carries a very distinct hazard of inducing neoplasia.[3] This hazard is much greater in very young individuals.[7] The development of nodules in the thyroid gland after the administration of therapeutic radioiodine to children has been reported.[8]

Radioactive iodine has not been used to treat hyperthyroidism in children at this hospital. We have seen, at another hospital, 1 case of carcinoma appearing in a child treated for hyperthyroidism with radioactive iodine. One adult operated upon at U. C. L. A. had a benign adenoma which appeared after treatment with radioactive iodine. In both of these cases the tumor appeared in a lobe of the thyroid which was diffusely homogeneous by radioiodine scanning and physical examination before the therapy.

A second major hazard of therapeutic radio-

active iodine is the production of the histologic and clinical appearance of Hashimoto thyroiditis.[3] There is clinical and experimental evidence that this is an autoimmunization reaction due to a globulin, probably thyroglobulin, from thyroid tissue breakdown.[1, 6] A significant experience with this situation has now accumulated and this can be listed as one of the definite sequelae of this form of therapy. The hazards of radioiodine in therapeutic amounts during pregnancy or lactation and the risk of possible genital injury have been noted in the literature.

Surgical treatment for hyperthyroidism, whether in a diffuse or a nodular goiter, has been declining steadily for at least a decade. During this time the surgical exploration of nontoxic nodular goiters has undergone both a relative and an absolute increase. There has also been a distinct increase in the absolute and relative incidence of malignant thyroid neoplasms and thyroiditis, particularly of the lymphadenoid variety.[5]

In this report we have excluded the cases of thyroglossal duct cysts. Of the 113 thyroid gland operations performed here, 81 have been done for adenomas or involutionary nodules of various types; 20 carcinomas and 1 case of Hodgkin's disease of the thyroid with extensive involvement of the neck structures have been found; 4 cases of "pure" thyroiditis have been operated upon and in 15 others some degree of parenchymal thyroiditis was noted, in conjunction with carcinoma. In addition to the 20 cases who had their primary surgical treatment at this institution, 7 cases of thyroid carcinoma have been seen who had their primary operations elsewhere. One of these cases had had a thyroid carcinoma treated by lobectomy 11 years previously. Exploration of the remaining lobe was undertaken at U. C. L. A. for a nodule which was "nonfunctioning" by scintigram. This proved to be an adenoma. There was no evidence of recurrence of the carcinoma in the neck or elsewhere.

One patient seen here for another medical condition had had a thyroid carcinoma treated by lobectomy at another institution 17 years previously. Approximately 6 months after the thyroid surgery she had developed a mass in the tonsillar fossa, which was found to be metastatic carcinoma of the thyroid. She was given a course of high voltage x-ray therapy at that time. When seen here 17 years later there was no evidence of recurrence of the thyroid carcinoma. She was on thyroid supportive therapy during most of this time.

One other case was extensively studied in our medical department because of purpura which developed during a pregnancy 2 years after removal of a thyroid carcinoma elsewhere. Extensive tests failed to reveal any definitive cause for her abnormal bleeding tendency. No connection could be shown between the thyroid lesion and its treatment and any of her subsequent problems. There has been no recurrence of the purpura or the carcinoma in the 2-year interval she has been under observation.

Two cases of thyroid carcinoma originally operated upon elsewhere had extensive metastases when first seen here. One of them was admitted for treatment of a myocardial infarction. This patient recovered and is still alive, although multiple bone metastases are known to be present. The other was admitted with a pathologic fracture of the femur, which was treated by intramedullary nailing here. He was discharged from this hospital after completion of this treatment and died 4 months later in another hospital of widespread carcinomatosis.

Three patients operated upon elsewhere had a thyroid carcinoma found at lobectomy or local excision of a nontoxic nodule. In each case a total thyroidectomy was done a few days later by the original surgeon. One of the cases had a bilateral radical neck dissection in two stages and 1 had a unilateral neck dissection. All of these patients were shown to have residual thyroid tissue in the neck capable of taking up radioactive iodine. The metabolic clinic and radiation laboratory undertook to destroy all of the remaining thyroid tissue with large doses of radioactive iodine. In 2 of these the remaining tissue was "encouraged" to take up the radioiodine by the use of thyroid-stimulating hormone. Total body scanning in 2 of them revealed no evidence of thyroid tissue outside the neck.

In all of the cases subjected to therapeutic radioiodine to destroy residual thyroid tissue, the treatment was successful, as judged by follow-up scanning. All of them received thyroid supplements by mouth.

THYROIDITIS

Thyroiditis was diagnosed in 4 cases after surgical excision of nodules in nontoxic goiters which proved to have little or no function by scintigram.

In 2 the surgery consisted only of removal of the isthmus and in 2 others subtotal thyroidectomy was done. They have all received thyroid supplements postoperatively.

The tissue slides of all of the cases of carcinoma have been reviewed in the light of the report by Meier and associates.[4] It was felt that the surrounding parenchyma was free of histologic evidence of thyroiditis in 5. "Minimal" thyroiditis was demonstrable in 10 and "moderate" thyroiditis in 5.

In 2 additional cases operated upon because of the fear of malignancy, thyroiditis was a prominent feature of tumors in which there is some difference of opinion among pathologists. They have been classed as adenomas although there is borderline evidence of histologic malignancy.

In a simultaneous survey of over 700 thyroid operations at two other hospitals in this area, thyroiditis was a parenchymal feature in 16 per cent (St. John's Hospital) and 17 per cent (Santa Monica Hospital) of the nontoxic thyroids removed. We have excluded all cases of hyperthyroidism in this review to eliminate any possibility that the lymphoid hyperplasia associated with that disease might distort the figures.

We must agree that thyroiditis is much more common than is generally supposed and that it is increasing disproportionately to other thyroid diseases.[5]

ADENOMAS AND INVOLUTIONAL NODULES

There were 81 operations performed for lesions which proved to be in this category on pathologic examination. Of this group 14 were treated by local excision of the nodule. Three of the nodules were in the isthmus with the remainder of the gland normal to inspection and palpation. In 4 cases there were multiple nodules in both lobes, all of which were treated by local excision. One patient had a "commando" operation for carcinoma of the tongue with bilateral metastases to the neck nodes. In the course of this operation a solitary nodule in the thyroid was encountered and removed; it proved to be an adenoma. There were 16 patients treated by subtotal thyroidectomy for nodules which proved to be either benign adenomas or involutional nodules. In 2 of these, as previously noted, Hashimoto thyroiditis was found in the surrounding parenchyma. In 51 cases adenomas or involutional nodules were found after lobectomy for nodular goiter, and in 1 of these a Hurthle cell adenoma with associated thyroiditis was found (previously noted).

One other Hurthle cell adenoma was found in a case of particular interest. At operation for a solitary nodule the thyroid lobe was removed, leaving a small fragment of tissue near the superior pole. Several months later a small nodule appeared in the region of the superior pole and enlarged slowly under observation. It was thought that this might represent a suture granuloma and the mass was explored under local anesthesia in the outpatient department. It was found to be of thyroid origin and the patient was admitted for exploration under general anesthesia. At operation 11 months after the first procedure this invasive mass proved to be a Hurthle cell carcinoma. The pathologists have re-examined the slides and agree that a diagnosis of malignant change cannot be made on the original tumor. The first lesion is a benign Hurthle cell adenoma and the second a Hurthle cell carcinoma.

One patient had a thyroid adenoma found at operation for multiple nodules in the neck, which proved to be metastases from a carcinoma of the lung. The adenoma was not related to the neck metastases. One patient, previously mentioned, had had a thyroid lobectomy elsewhere for cancer; at exploration here for a nonfunctioning nodule of the remaining lobe a follicular adenoma was found.

CARCINOMA

In this series, 20 cases of thyroid carcinoma had their primary surgical treatment at this hospital. One additional case was considered on preoperative studies to have carcinoma with extensive neck metastases. At surgery the tumor was so invasive that complete extirpation was impossible. The tumor proved to be Hodgkin's disease, probably primary in the thyroid, with extensive involvement of the neck structures. Further treatment was by radiation.

One patient was explored for a nonfunctioning nodule of the right lobe demonstrated by scintigram. At surgery an unsuspected small cystic lesion was found at the lower pole of the left lobe. The nodule of the right lobe proved to be an adenoma and was treated by lobectomy. The cystic lesion of the left lower pole was removed by local excision and on final section was found to be a papillary carcinoma. The patient has been on suppressive therapy with 3 grains of desiccated thyroid daily since that time. Follow-

up scintigrams (after temporary interruption of the drug) reveal that there is no functioning thyroid tissue left on the right (adenoma) side. The left lobe remnant seems to be homogeneous, functions normally, and is of normal size and contour. The patient has steadfastly refused further surgery and no evidence of metastasis has appeared in the 2 years she has been followed. This was the only case of thyroid carcinoma treated by local excision of the lesion.

Twelve cases of thyroid carcinoma, chiefly papillary or mixed papillary and follicular, have been treated by lobectomy. We have previously noted the presence of thyroiditis in the surrounding parenchyma. In 1 of these 12 cases a radical neck dissection was done on the affected side and postoperative radiation was given using the cobalt bomb. The opposite thyroid lobe was considered normal and was not removed.

It is of interest that in 4 of the cases treated by lobectomy the carcinoma cells were found to extend close to the limit of resection. There have been no clearly demonstrated multicentric carcinomas within the thyroid substance or intrathyroid metastases, other than invasion of blood vessels or the "capsule."

It has been the practice at this center to perform the lobectomy including the isthmus and no "routine" removals of the opposite lobe or "routine" neck dissections have been done. These patients have been given oral thyroid substance after the surgery in only a few cases and for relatively short periods. No postoperative radiation has been used in this group of cases. There have been no instances of parathyroid deficiency or recurrent laryngeal nerve damage in the cases of carcinoma treated by lobectomy.

The choice of surgical treatment in most of these cases has been made in the operating room after frozen section confirmation of the diagnosis has been obtained. In a few cases the final diagnosis of carcinoma could not be determined until the permanent tissue sections were available, but none of those treated by lobectomy in this situation were subjected to further extirpation of the gland.

In 7 of the cases of carcinoma who received their primary surgical treatment at this center a total thyroidectomy was done. One of these patients had a needle biopsy done before surgery, the only case in which this technique was used. In 2 of the 7 cases a radical neck dissection was done on the affected side at the time of the total thyroidectomy. In 2 others the second side was subjected to radical neck dissection 3 to 6 weeks after the total thyroidectomy and neck dissection of the primary side. Every case subjected to radical neck dissection, unilateral or bilateral, was found to have metastatic involvement of the resected nodes. No case was subjected to a bilateral neck dissection at a single operation. One patient had a temporary tracheostomy after the second radical neck dissection.

Of the patients subjected to total thyroidectomy, 3 were given postoperative therapeutic doses of I^{131} to eliminate any remnants of functioning tissue found on scanning after thyroid-stimulating hormone. Two others had no evident functioning tissue on scanning after surgery and 1 other received postoperative radiation with the cobalt bomb.

Every one of the 7 cases subjected to the total thyroidectomy had some difficulties with hypoparathyroidism after surgery. This responded over a period of some weeks to therapy with calcium, parathyroid hormone or AT10, but in 2 cases persistent hypoparathyroidism has been a problem. In 2 cases one of the recurrent laryngeal nerves was deliberately sacrificed because of the involvement by the cancer; no other permanent nerve damage was encountered in the group of cases.

We now feel that the high incidence of parathyroid deficiency, the technical difficulties of preserving the nerves and parathyroids without leaving behind any thyroid tissue and the fact that the tiny remnants of functioning thyroid tissue so commonly left behind are susceptible to destruction by radioactive iodine all combine to indicate that a radical subtotal removal is preferable to a "total" thyroidectomy. The remnants can probably be destroyed by radioiodine more safely than they can be extirpated surgically. The underlying philosophy of the choice of treatment in thyroid carcinoma has recently been explored in an excellent study from the Memorial Hospital.[2]

No general agreement exists on whether these patients should be treated postoperatively with thyroid or with triiodothyronine. Thyroid has been used in most cases and temporarily discontinued when scanning was done.

SUMMARY

The experience in thyroid surgery at the U. C. L. A. Medical Center over the last 3 years

includes 113 thyroid operations. Hyperthyroidism at this institution has been treated by radioactive iodine in the majority of cases. Some dangers inherent in this method of management are noted. Some degree of thyroiditis in the parenchyma was revealed in 20 per cent of the thyroid specimens. Malignant thyroid neoplasms were found in 19 per cent of the cases. In the majority of this group of cases the nature and extent of the disorder was not correctly diagnosed preoperatively. The majority of the patients with thyroid carcinoma who received their primary surgical treatment here were treated by lobectomy without subsequent radiation, neck dissection or oral thyroid therapy. Every patient subjected to total thyroidectomy had transient postoperative hypoparathyroidism; 2 have had persistent hypoparathyroidism.

The scanning "scintigram" has yielded valuable information regarding nodular areas in various thyroid disorders and in detecting residual thyroid tissue after surgical extirpation. There has been no mortality associated with any thyroid operation in this series. There have been no instances of postoperative hemorrhage or infection. The high incidence of malignancy in this series undoubtedly represents a large element of selection in the case material referred for surgery at this center.

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Dr. William F. Pollock
University of California Medical Center
Los Angeles 24, California

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THE PATHOLOGIC ANATOMY OF RETINAL DETACHMENT*

BRADLEY R. STRAATSMA, M.D.

Los Angeles, California

Although accepted by general usage, the term "retinal detachment" is a misnomer in the sense that the retina as a whole is not involved. The process, in reality, is a splitting that occurs between two layers of the embryonic optic cup. As a result, the delicate and friable sensory portion of the retina is separated while the pigment epithelium of the retina remains in contact with the underlying choroidal tissue. It would seem that displacement of this highly differentiated piece of tissue, no larger in area than the skin covering the ball of one's thumb,[1] would offer few variations. The actual picture, however, is one of great complexity, with infinite variation in the factors of incidence and etiology, the features of clinical course, and the characteristics of pathologic anatomy. In incidence, the disorder may be unilateral or bilateral, and span the extremes of age with an onset in infancy or later life. The etiology encompasses all major forms of disease including congenital abnormalities, inflammatory disorders, degenerative conditions, traumatic insults and neoplastic processes.

With this broad spectrum of incidence and etiology, it is not surprising that retinal detachment is, in essence, a multiple disease that is not a single pathologic entity but an anatomical accident that may result from several causes during the course of many diseases. In view of this diverse etiology, appraisal of the pathologic anatomy of retinal separation may develop logically from an evaluation of the mechanical aspects of the tissue changes. From this consideration it is manifest that retinal detachment may result from a subretinal mass pushing the sensory layers from their normal position, from mechanical forces in the vitreous exerting traction and pulling the retina from its normal position, or from inherent retinal disease. These factors, singly or more frequently in combination, may result in retinal separation.

However, before considering any disease process or mechanical sequence responsible for detachment, reference should be made to the normally weak union which exists between the sensory retina and the retinal pigment eipthelium. Standard texts state that the two layers merely lie in apposition to one another and are joined anatomically only at the optic disc and at the ora serrata. This is not entirely true, however, because a recently demonstrated acid mucopolysaccharide surrounds the rods and cones of the sensory retina and joins these elements to the pigment epithelium. This material resists digestion by hyaluronidase and is similar in staining properties to the substance uniting the analogous layers of the ciliary body and iris.[8] The function of this mucopolysaccharide is not known, but it may serve as a medium for metabolic exchange or have an optical effect essential for certain acts of visual perception. Regardless of its function, it is known that this material does not tightly bind the sensory retina to the pigment epithelium because an artifactitious detachment of the retina is a common result of gross sectioning and the histologic preparation of normal eyes. This artifactitious detachment can be distinguished from an *in vivo* separation of the retina by the absence of subretinal material, the normal structure of the rods and cones in the detached retina, and the absence of retinal tears, vitreous traction, or other general abnormalities responsible for the sequence of retinal detachment (fig. 1).

The weak union between retinal layers that permits this artifactitious detachment also facilitates separation *in vivo* as a result of subretinal mass or fluid exudation in the subretinal space. Hemorrhage between the pigment epithelium and the sensory retina may be responsible for retinal separation, or it may contribute to a detachment initiated by other factors. The presence of such a discrete mass of blood may simulate the clinical appearance of a tumor and lead to an erroneous diagnosis and possible enucleation of the globe. This differential is complex when subretinal hemorrhage occurs as an isolated feature. Generally, however, this bleeding in the subretinal space occurs in association with other retinal diseases such as Coat's disease.[5] In this

* From the Department of Surgery, Division of Ophthalmology, University of California Medical Center, Los Angeles, California.

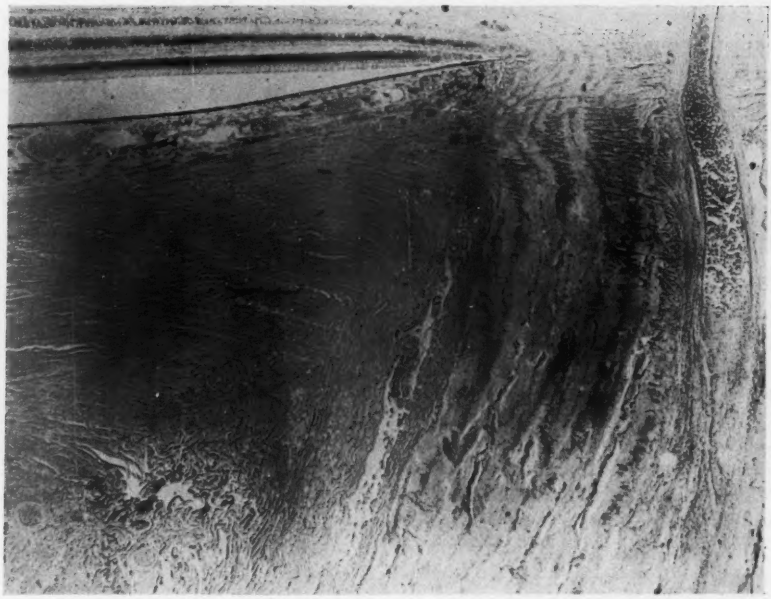

FIG. 1. Artifactitious retinal detachment that developed during the process of gross sectioning and histologic preparation, hematoxylin-eosin, × 21. From the Armed Forces Institute of Pathology, Acc. No. 47846.

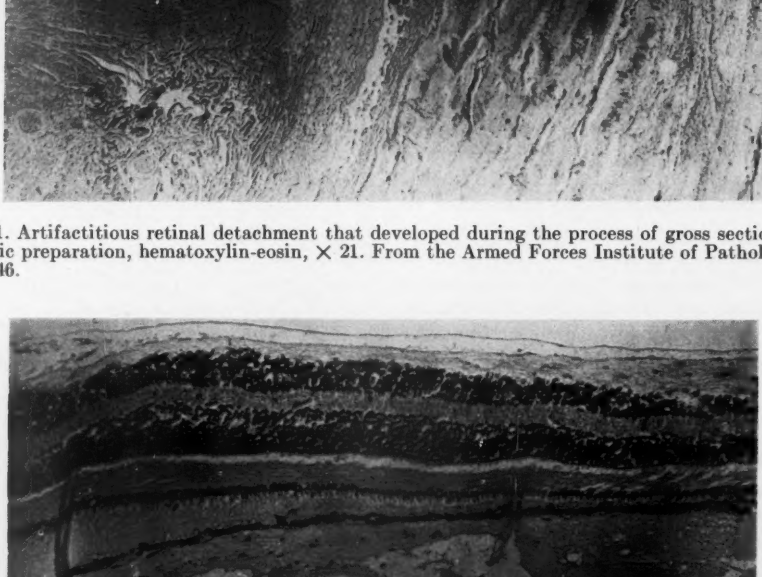

FIG. 2. Serous detachment of the macula with separation of the retinal pigment epithelium from the choroid (Kuhnt-Junius juvenile type), hematoxylin-eosin. From the Armed Forces Institute of Pathology, Acc. No. 685300.

circumstance, the general alteration in retinal structure and the predilection for a unilateral development in young males, facilitates the diagnosis. Another cause of subretinal hemorrhage is the disturbance of retinal structure and function associated with diabetic retinopathy. Here again, the systemic features of the disease and the concurrent ocular alterations permit reliable diagnosis.

A purely exudative extravasation in the retinal space is seen in detachment associated with toxemia of pregnancy, some forms of uveitis, central angiospastic retinopathy (central serous choroiditis), and the Kuhnt-Junius type of juvenile disciform macular degeneration. The latter is a somewhat unusual form of exudative detachment in that most of the fluid is located between the choroid and the retinal pigment epithelium and only a small amount of exudative material separates the retina from the pigment epithelium (fig. 2). Diagnosis of this and other forms of exudative retinal detachment is of the greatest clinical importance becuse prompt reversal of the process is consistent with restoration of retinal function. However, the severe uveal inflammation associated with Harada's disease and exudative tuberculous and syphilitic uveitis may precipitate destruction of the globe and warrants a guarded prognosis.

A number of tumors, such as choroidal malignant melanomas, retinoblastomas, and metastatic growths, may also occupy the subretinal space and produce retinal detachment. Malignant melanomas are confined to the choroid during their initial development and, subsequently, may rupture through Bruch's membrane to expand into the subretinal space. Rarely, these tumors break through the retina, but generally the retina remains intact and is separated from the tumor by a variable amount of exudative material. This exudation may be minimal in degree or sufficient to produce a large bleb of detached retina in a remote portion of the ocular fundus, and is always increased in amount when the tumor undergoes inflammation or necrosis. As with any other form of detachment the segment of retina overlying the tumor is deprived of nutrition and consequently develops degenerative and cystic changes which may be evident clinically as retinal hemorrhages, an extensive vitreous extravasation, or a defect in the field of vision (fig. 3).[3]

The retinoblastoma is another type of ocular tumor which may produce retinal detachment by expanding into the potential space between the sensory retina and the pigment epithelium. This growth is primary in the retina and is capable of extension into the vitreous space or progression into the subretinal area. This form of retinal detachment may then mask a malignant tumor and, just as in the case of the choroidal melanoma, discovery and surgical removal may be a life-saving measure.

Tumors metastatic to the eye are usually a consequence of carcinoma primary in the breast or lung and show a predilection for location in the choroid near the posterior pole. These lesions progress slowly or rapidly to massive size and are associated with complete detachment of the retina. Appropriate diagnosis is important because of the frequent binocularity of metastatic tumors and the advantages of x-ray therapy as a palliative measure.

The second major form of retinal detachment is the result of traction which pulls the retina from its normal position and focuses attention on the vitreous body. This transparent tissue, filling the major inner chamber of the eye, is a multicomponent, fine gel containing scattered cells and consisting of 98.7 per cent water and macromolecular components; specifically, fibrous protein, glycoprotein, blood protein, and hyaluronic acid.[7] Anteriorly, this vitreous body is joined to the posterior lens capsule and to the ciliary body by weak attachments. The base, or main attachment of the vitreous, occupies an area approximately 2 mm. broad which extends over the posterior pars plana and the ora serrata. This attachment is so firm that attempts to separate the vitreous base cause shreds of epithelium to be torn from the ciliary body and ora. Normally, this vitreous gel fills the posterior segment of the globe and a union exists between the sensory retina and the vitreous body (fig. 4). This union has received insufficient attention, although its development can be readily understood by a consideration of normal embryologic development and appreciation of the fact that the vitreous body develops to a large extent from the sensory retina.[8]

This continuous and consistent union between the vitreous and the sensory retina is stressed because we know that the vitreous is not static throughout life. It probably undergoes twisting

and churning with every motion of the eye, and certainly undergoes gross changes in senescence and disease. A consideration of vitreous abnormalities related to retinal detachment should include reference to embryonic remnants in the vitreous, invasion by exogenous foreign elements, the presence of endogenous foreign elements in the vitreous body, and alterations of the vitreous gel.

The complex and remarkable embryonic development of the vitreous body includes derivation of this structure from surface ectoderm, neural ectoderm of the optic cup, and mesoderm. Thus, it is not unusual to find remnants of this developmental sequence in the adult vitreous. These persistent structures, such as cataracta spuria, the arc line on the posterior lens capsule, and muscae volintantes, are frequently encountered in otherwise unremarkable eyes. However, embryonic residua may range in severity from these normal variations to a severe developmental abnormality known as persistent hyperplastic primary vitreous.[4] This condition generally presents as a unilateral leukocoria, or white pupil, in a somewhat microphthalmic eye that histologically shows a plaque of vascularized fibrous tissue on the posterior lens surface and a persistent hyaloid vessel passing from this mass to the optic disc. In these cases, the retina may be uninvolved and remain in normal position. However, in more advanced stages of this developmental abnormality, the retina adheres to the hyperplastic primary vitreous and a congenital retinal fold or total retinal detachment results. The retina involved in the congenital fold or total

FIG. 3. Two separate choroidal malignant melanomas and one nevus of the choroid with secondary detachment of the sensory retina, hematoxylin-eosin, × 2. From the Armed Forces Institute of Pathology, Acc. No. 846169.

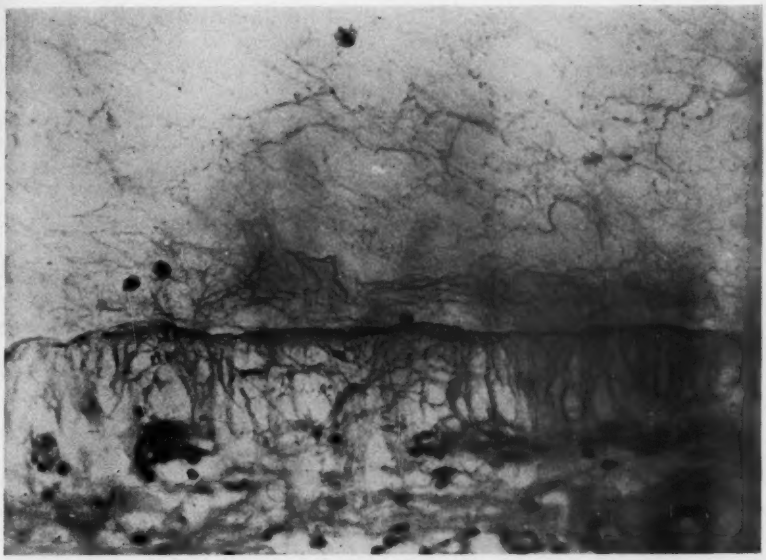

FIG. 4. Normal anatomical union between the vitreous and sensory retina showing cells in the cortex of the vitreous. Alcian blue stain for acid mucopolysaccharide. From the Armed Forces Institute of Pathology, Acc. No. 793831.

detachment shows abnormal differentiation, gliosis, and a characteristic pattern of rosettes. The rosettes of this retinal dysplasia consist of a rod and cone layer, inner limiting membrane and nuclear layer, but are readily distinguished from the rosettes of retinoblastoma by their irregular shape and greater size (fig. 5).[6]

Invasion of the vitreous body is followed by a permanent disruption in vitreous structure. Parasites or foreign bodies passing through the vitreous leave a permanent track which can be detected and may subsequently organize to result in traction on the retina. Endogenous cellular or acellular material may also invade the vitreous body and initiate the sequence of organization and contraction. This organized cyclitic membrane generally attaches to the ciliary body and anterior retina so that subsequent condensation and contraction may produce a funnel shaped retinal detachment with virtual obliteration of the vitreous space (fig. 6).

Hemorrhage in the vitreous body is another form of endogenous cellular invasion which is all too frequently the forerunner of organization, contraction, retinal traction, and detachment. Organization of a vitreous hemorrhage is generally associated with the development of retinitis proliferans, a neovascularization and proliferation extending from the nerve head or the retina into the gel structure of the hyaloid body. Diabetic retinopathy is a common cause of hemorrhage, retinitis proliferans and detachment, although other forms of retinal disease and vitreous hemorrhage can precipitate retinal separation. Although sporadic examples continue to develop, discovery of the relationship between oxygen and retrolental fibroplasia has markedly decreased this cause of hemorrhage, retinal detachment, and blindness in premature infants.

Consideration must also be given to alterations of the vitreous gel which are so important to an understanding of serous or "idiopathic" detachment of the retina. Many of these changes are poorly understood and clarification awaits knowledge of physical structure and chemistry. It does seem likely, however, that alterations such as syneresis, fiber development, membrane formation, and shrinkage occur to some extent as senescent changes, but are distinctly accentuated by disorders such as inflammation, trauma and myopia.[7]

Syneresis, or liquefaction of the vitreous gell, is recognized clinically by the appearance of optically clear spaces devoid of normal diaph-

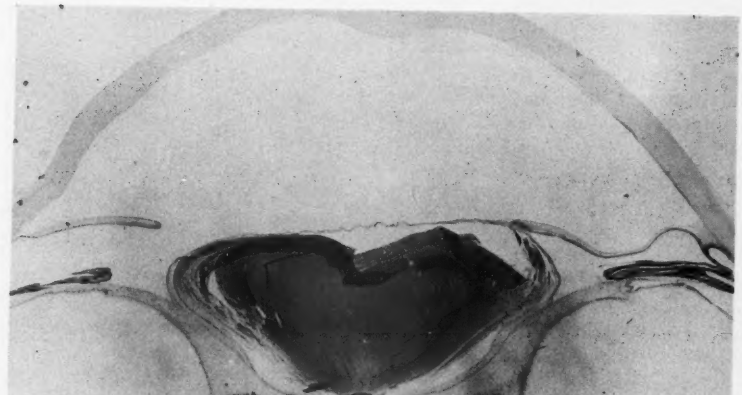

FIG. 5. Retinal dysplasia with detachment and abnormal differentiation of the sensory retina, hematoxylin-eosin, × 6. From the Armed Forces Institute of Pathology, Acc. No. 846393.

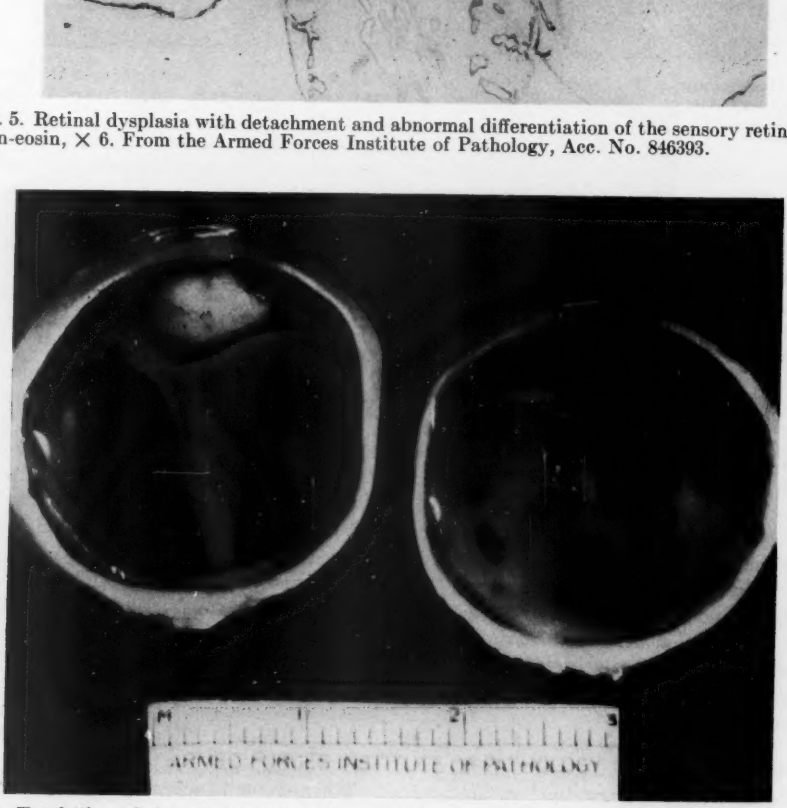

FIG. 6. Total "funnel shape" retinal detachment with macrocyst in an eye with uveitis sequelae and a cyclitic membrane. From the Armed Forces Institute of Pathology, Acc. No. 867080.

anous structure when the vitreous is studied with a slitlamp.[2] This liquefaction of the vitreous is also evident during certain surgical procedures, is apparent when affected eyes are opened for histologic sectioning, and disclosed by special staining techniques which demonstrate the absence of the usual regular mucopolysaccharide structure. This liquefaction is most frequently encountered in the central portion of the vitreous, although it may involve the cortex or be evident on the surface of the retina (fig. 7).

This careful consideration of syneresis assumes significance when it is co-ordinated with the probable activity of the cells in the vitreous body. The precise origin of these cells is not known. However, they are present during embryologic development and in the adult eye, and seem capable of forming membranes along the pockets of syneresis (fig. 8). It is these newly formed membranes which exert traction on the retina and probably account for the fixed and rigid folds of a detached retina. As such, this sequence of liquefaction and membrane formation is contributory to the initial retinal detachment and to the further structural alterations which may unfavorably influence surgical management.

The presence of other vitreous alterations such as gross membranes or bands of condensation and the appearance of coarse fibers in the vitreous structure are readily detected clinically and histopathologically. These bands are common sequelae of contusion, inflammation and intraocular hemorrhage, and may be traced to the retinal surface.

These vitreous changes, syneresis, membrane formation, and the appearance of bands in the vitreous gel do no major harm to the eye until shrinkage of the vitreous body takes place. Then inexorable and progressively severe contraction tends to pull on both the normal and the abnormal retinovitreal adhesions. Traction on the normal attachment of the vitreous to the optic nerve head may produce a blurring and elevation of the disc margins akin to pseudopapilledema. Shrinkage of the vitreous gel at the posterior pole may cause macular distortion and edema with the associated symptoms of metamorphopsia (*i.e.*, the distortion of objects) and central photopsia.

When abnormal retinovitreal adhesions in the equatorial area are associated with shrinkage and detachment of the vitreous, the resultant

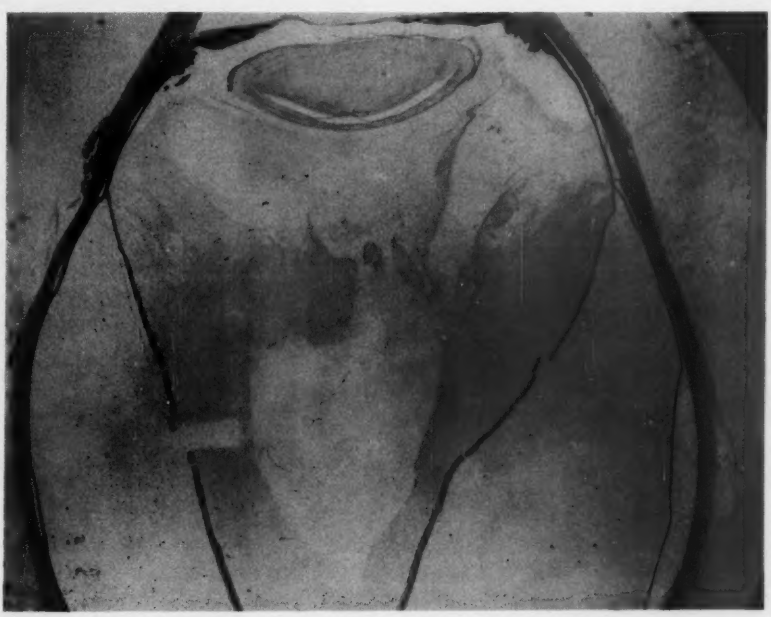

FIG. 7. Syneresis or liquefaction of the central vitreous. Tissue stained with Alcian blue to demonstrate acid mucopolysaccharide. From the Armed Forces Institute of Pathology, Acc. No. 500486.

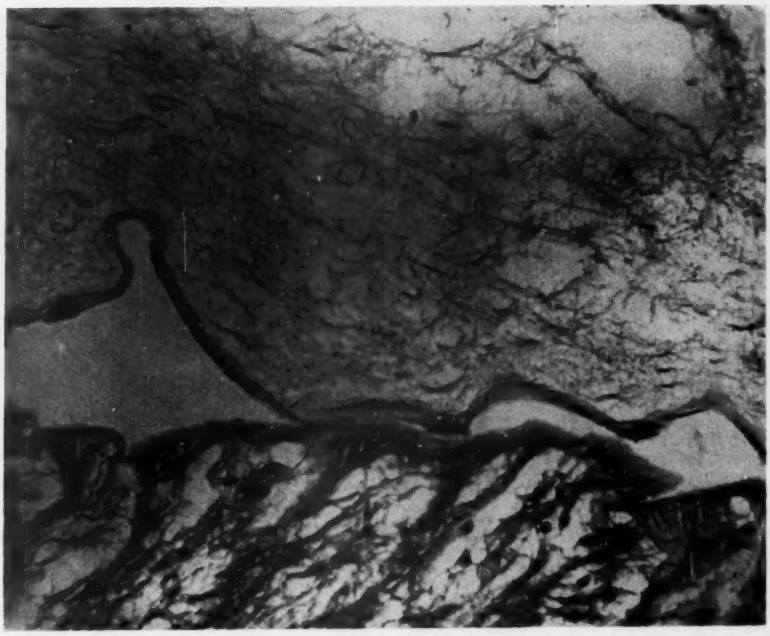

FIG. 8. Degeneration of the retinal-vitreous union with formation of a membrane on the surface of the vitreous. Acid mucopolysaccharide stain, × 220. From the Armed Forces Institute of Pathology, Acc. No. 833505.

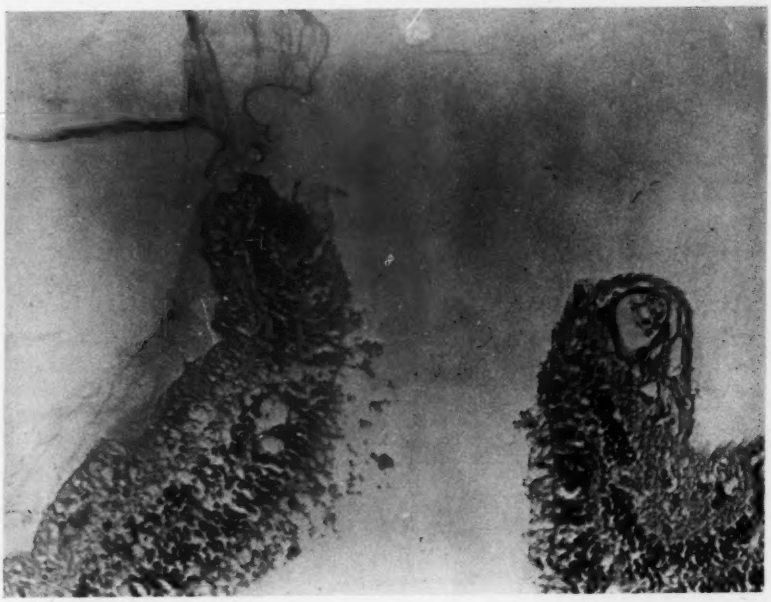

FIG. 9. Retinal tear with vitreous attached to the flap of retina, Alcian blue, × 34. From the Armed Forces Institute of Pathology, Acc. No. 859545.

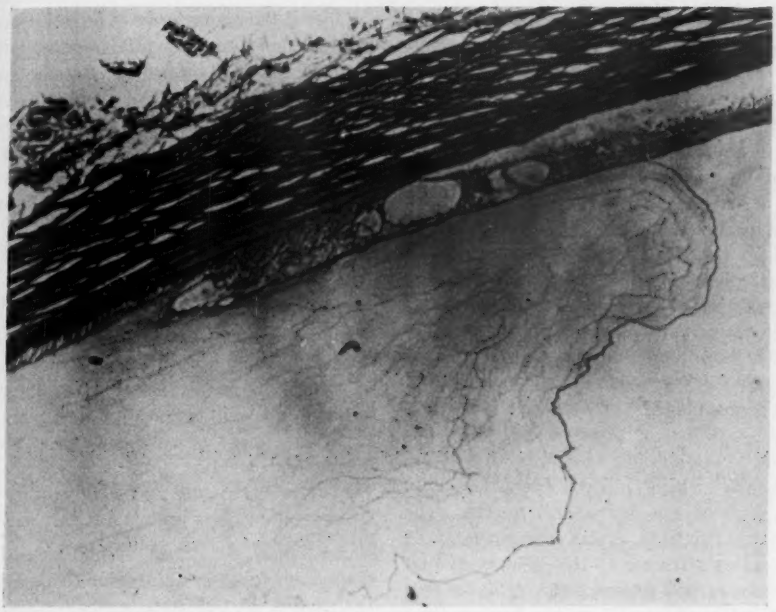

FIG. 10. Cystoid spaces in the peripheral retina, acid mucopolysaccharide stain, × 10.3. From the Armed Forces Institute of Pathology, Acc. No. 858425.

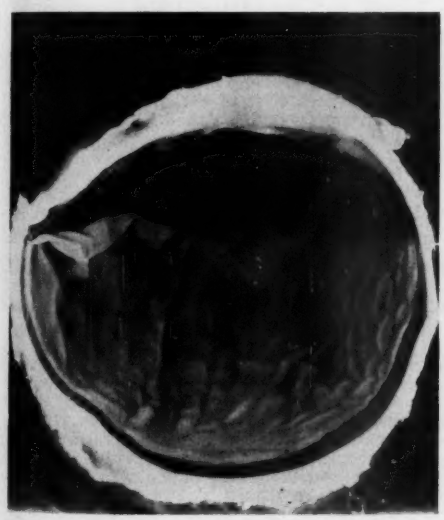

FIG. 11. Traumatic disinsertion of the retina and avulsion of the vitreous base. From the Armed Forces Institute of Pathology, Acc. No. 878955.

mechanical irritation stimulates the retina and produces the sensation of light flashes. Further traction, particularly when acting on a degenerated portion of the retina, may produce a retinal break or tear. This tear generally extends in the direction of least resistance and leads to a horseshoe shaped rupture. With the magnification of histopathologic sections and the assistance of special staining techniques, the sharp edge of the retinal tear with a strand of attached vitreous can be seen projecting into the hyaloid space (fig. 9). As a result of this retinal tear, fluid from the vitreous can then percolate behind the retina and separate it from the retinal pigment epithelium and choroid. Once initiated, this process tends to progress to complete retinal detachment.

Appreciation of these vitreous changes is essential to an understanding of the pathogenesis of serous detachment, but other factors are significant in this complex sequence. Notable are characteristics of the retina itself. This thin and highly organized, friable layer is dependent on a dual blood supply. The nourishment of its inner portion is derived from the central retinal artery and its branches. The vascular supply for the rod and cone layers and external connecting units is obtained from the richly vascular choriocapillaris. This relatively precarious and finely balanced vascular supply is probably to some extent responsible for the tendency of the retina to undergo cystic degeneration. These cystic

spaces arise, particularly in the peripheral retina, as vacuoles in the inner nuclear and outer plexiform layers (fig. 10). They subsequently enlarge and coalesce to produce cystoid spaces which represent weakened areas in which the retina is prone to rupture. This predilection for cystic degeneration may thus contribute to the sequence of retinal detachment initially, and certainly partakes in the degeneration which develops in the detachment of the retina. In some examples of retinal detachment, these cystic spaces may assume giant dimensions and pose an obvious therapeutic problem. More commonly, however, they do produce one or more "secondary" round holes in the detached retina. The macular area, if detached, is particularly prone to cystic degeneration, and this alteration is responsible for the diminished visual acuity which follows even successful reattachment of the retina and macula. The complexity of retinal cystic change may be emphasized by reference to the giant cysts that develop in attached retinas early in life or as a senile alteration. These idiopathic degenerations have been given the designation of retinocele when one large chamber is present and retinoschisis when several communicating large cavities within the retina are detected.

Trauma has not been specifically cited in this review, but it may predispose to detachment of the retina, or precipitate this event by producing alterations in the vitreous gel, vitreous hemorrhage, contusion of the retina, retinal tears, or subretinal hemorrhage. A specific form of detachment associated with trauma is the disinsertion or rupture of the retina at the ora serrata. These large dehiscences are often present in younger patients and generally follow severe ocular contusion. This contusion is associated with marked distortion of the globe at the moment of injury and rupture of the vitreous base from its attachment to the pars plana and ora serrata with concomitant laceration of the peripheral retina (fig. 11).

This evaluation of pathologic anatomy has considered the major forms of retinal detachment with reference to congenital lesions, inflammation, degenerative disorders, trauma and neoplasms. It has illustrated the features shared by these diverse disorders and has emphasized the characteristics dictated by the anatomy of the structures involved. This framework of histopathology provides a logical approach to diagnosis and appropriate therapy.

SUMMARY

This review has presented pertinent features of the normal anatomy of the sensory retina and its relationship to adjacent structures. This relationship is readily disturbed by the artifacts of histopathologic preparation, but more significantly it is upset by subretinal space occupying lesions and traction from the vitreous body. The delicate, friable, and highly differentiated sensory retina plays an integral part in the complex interplay of these factors.

University of California Medical Center
Los Angeles 24, California

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MUCUS-SECRETING ADENOCARCINOMA OF THE URINARY BLADDER SIMULATING CARCINOMA OF THE GASTROINTESTINAL TRACT*

CHESTER C. WINTER, M.D., AND WILLARD E. GOODWIN, M.D.

Los Angeles, California

The discovery of a mucus-secreting adenocarcinoma in the urinary bladder usually raises the question of its origin. It is important from the standpoint of difference in treatment and prognosis to distinguish between cancer arising in the gastrointestinal tract and that arising in the bladder. This can be accomplished only by a more thorough study of the gastrointestinal tract than is ordinarily carried out for transitional and squamous cell carcinomas of the bladder.

Experience with 5 instances of mucus-secreting adenocarcinoma of the urinary bladder discovered during the past 10 years forms the basis of this communication. The rarity of these neoplasms is emphasized by the scarcity of similar case reports.

CASE REPORTS

Case 1. C. O. (WGH-42025), a 69-year-old white man, was admitted to the Medical Service on August 26, 1953, complaining of painful and rapidly progressing lower abdominal enlargement and decreased caliber of stools. Also, he had noted gross hematuria for 2 weeks. An abdominal fluid wave was palpable and rectal examination revealed a large mass presenting anteriorly, simulating Blumer's shelf. The differential diagnosis rested between carcinoma of the prostate, bladder, or rectum.† Three serum acid phosphatase determinations were normal. No bone lesions were visible by roentgenography. The mass, which was successfully outlined by barium, impeded proctoscopy. Both biopsy of the rectal mucosa and needle biopsy of the prostate failed to show neoplasm. Upper gastrointestinal and gall bladder roentgenograms were normal. A left hydronephrosis could be depicted by excretory urography. Cystoscopy exposed marked infiltration of the posterior bladder mucosa with multiple papillary tumors. The pathologist, Dr. Leo Kaplan, described the biopsy specimen from the bladder as "highly malignant epithelial tumor exhibiting signet cell simplex features (mucin-secreting). This unusual neoplasm, if derived from bladder or adjacent structures, certainly represents a unique primary neoplasm. It is, however, quite possible. One must rule out extension of neoplasia from the gastrointestinal tract" (fig. 1, *upper*). A repeat needle biopsy of the prostate as well as examination of the ascitic fluid disclosed similar neoplastic cells (fig. 1, *lower*). The patient died 4 months after admission and autopsy revealed a primary bladder tumor. The gastrointestinal tract was not involved.

Case 2. J. D. (JHH-381171), a 57-year-old Negro man, was first seen in 1946 complaining of weakness and gross hematuria. A large papillary bladder tumor was found by cystoscopy and was biopsied. It was diagnosed as adenocarcinoma arising from the colon, and x-irradiation was administered. He was readmitted to the hospital 2 years later, in May 1948, because of gross hematuria. Exploratory laparotomy revealed a tumor thought to be rectal in origin and inoperable. The pathologist gave the following report of the biopsy specimen: "The small fragments said to be from the bladder did not represent at all the usual picture of a bladder carcinoma. There is a papillary appearance, but the cells are large and darkly stained and tall columnar in variety. They frequently contain mucus in their cytoplasm and appear for all the world like a poorly differentiated adenocarcinoma of the large intestine. They are apparently infiltrating smooth muscle. Diagnosis: bladder; poorly differentiating adenocarcinoma with infiltration of muscle. Origin of tumor from large bowel or bladder." The patient was dismissed from the hospital, but because of continued hematuria, dysuria and difficulty in urination was readmitted in October 1948. A large, fixed, suprapubic mass was palpable. In addition, a hard, fixed mass was encountered in the bladder region by rectal examination. His blood pressure was 190/110 mm. Hg, hemoglobin was 11 gm. per cent and nonprotein nitrogen was 47 mg. per cent. The chest roentgenogram was normal. An intravenous urogram faintly outlines

* From the Department of Surgery, Division of Urology, University of California Medical Center, Los Angeles; Wadsworth General Hospital, Veterans Administration Center, Los Angeles; and the Los Angeles County Harbor General Hospital, Torrance, California.

† This case was discussed in an article by C. C. Winter: Prostatic cancer involving the rectum: the problem of differentiation from other malignant lesions. California Med., *82:* 85, 1955.

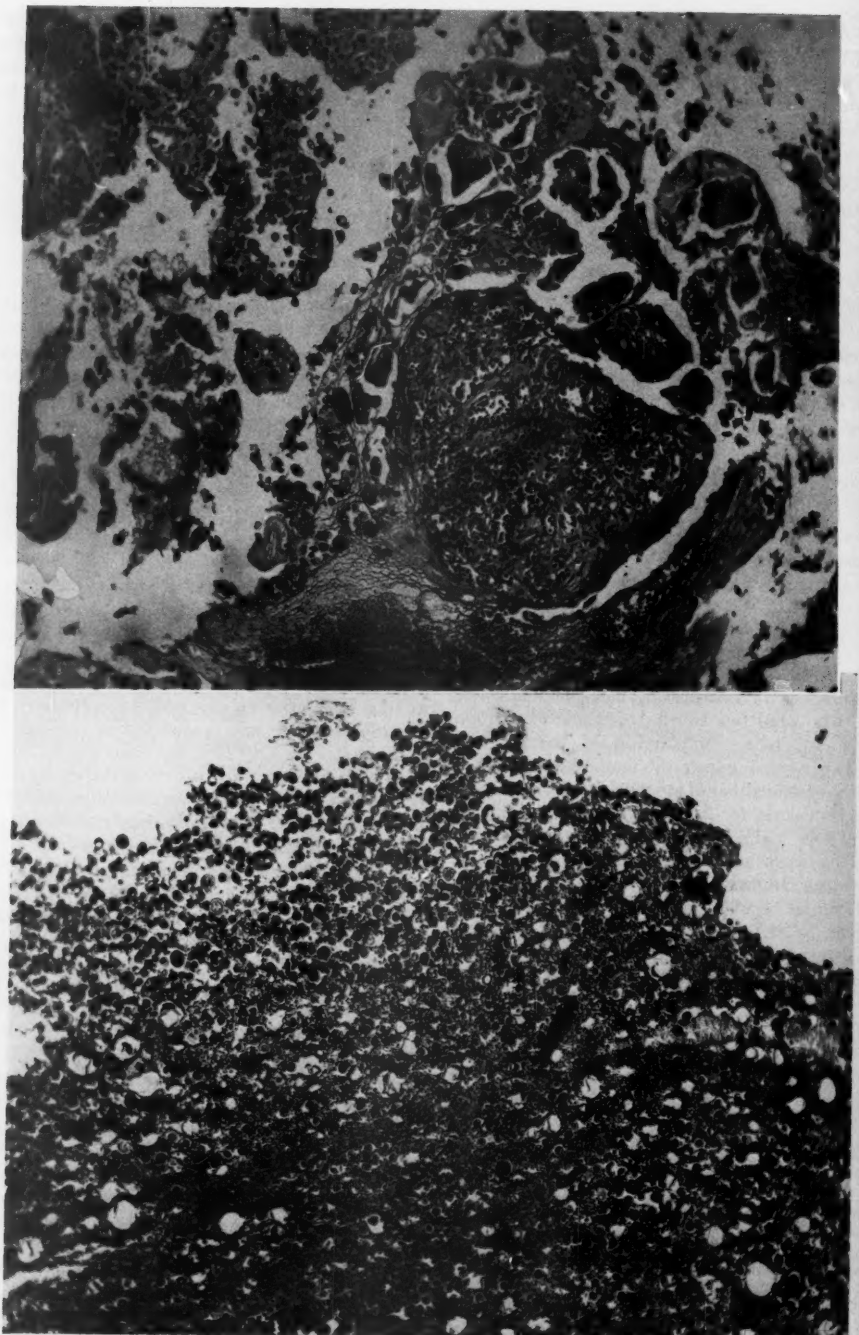

FIG. 1. *Upper*, mucus-secreting adenocarcinoma of bladder (case 1). *Lower*, ascitic fluid reveals signet cells of mucus-secreting adenocarcinoma (case 1).

a left hydroureteronephrosis, whereas the right upper urinary tract was not visible. The rectum and sigmoid colon could not be distended with barium due to constriction by a mass. Cystoscopy and transurethral biopsy of the bladder tumor were performed. A radical cystectomy, left ureterosigmoidostomy, ligation of the right ureter and an appendectomy were performed on October 13, 1948 (fig. 2). The pathologist reported that an adenocarcinoma involved the bladder trigone without evidence of extension. The patient was still living and well in 1957, 9 years later.

Case 3. H. P. M. (WGH-59447) was a 58-year-old white man who was admitted to the hospital in June 1956 with complaints of increasing frequency, urgency and weak force of urinary stream of 6 months' duration. These symptoms were accompanied by anorexia and loss of weight. The urine contained many white blood cells. On rectal palpation, a hard, irregular, fixed mass was felt in the area occupied by the seminal vesicles and prostate. Several examiners believed that the lesion was an extensive primary prostatic neoplasm. However, bone roentgenograms and several serum acid phosphatase determinations were normal. A narrowing of the rectum was outlined by barium. Nevertheless, sigmoidoscopy was reported as negative for 25 cm. Delayed excretory urograms revealed bilateral hydroureters and hydronephroses. Cystoscopy exposed an enlarged, firm prostate and a tumor involving the bladder neck, trigone and ureteral orifices. At this point the cystoscopist felt that the diagnosis could be either prostatic carcinoma invading the bladder or the reverse. The pathologist added a third possibility by stating that the needle biopsy of the prostate and cup biopsy of the bladder tumor appeared to be mucus-secreting adenocarcinoma arising in the bowel. On October 26, 1956, a radical cystectomy, including prostatoseminovesiculectomy and bilateral ureteroileocutaneous anastomoses (Bricker procedure), was performed. The pathologist reported that the tumor involving the trigone and bladder neck was a 5- by 6-cm., mucus-secreting

FIG. 2. A papillary mucus-secreting adenocarcinoma is seen arising from the trigone in upper portion of opened bladder; prostate and bladder neck are at top (case 2).

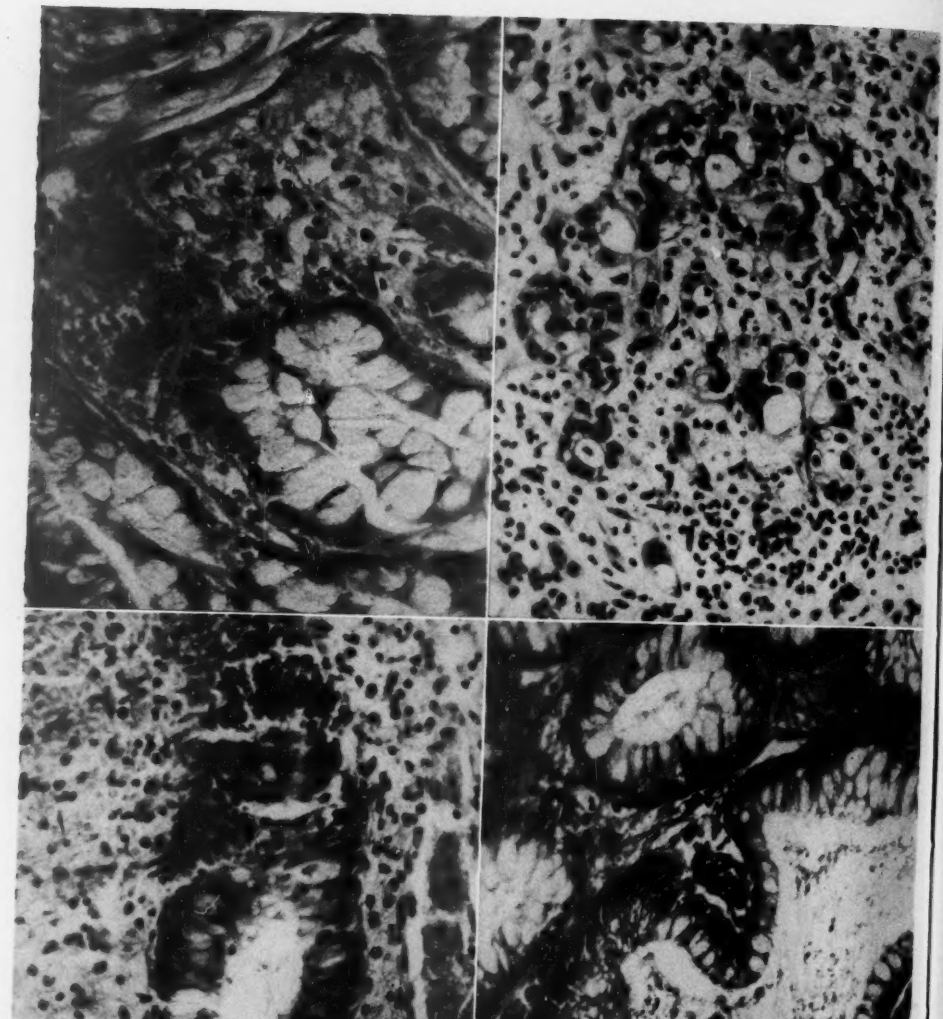

FIG. 3. *Upper left*, adenocarcinoma of bladder with large cells choked with mucus. *Upper right*, mucus-secreting adenocarcinoma of bladder (case 5). *Lower left*, biopsy of bladder tumor reported as cystitis glandularis (case 6). *Lower right*, rebiopsy of bladder tumor now diagnosed as mucus-secreting adenocarcinoma, later found to arise in sigmoid colon (case 6).

adenocarcinoma of the bladder extending into the seminal vesicles and prostate. A gradual downhill course followed and the patient died 6 months after admission of metastatic carcinoma of the lungs.

Case 4. W. D. R., Jr. (WGH-65089), a 46-year-old Negro man, was admitted to the Urological Service complaining of right flank pain of 5 hours' duration on July 20, 1957. Other symptoms consisted of hematuria, dysuria, fever and increasing frequency of urination. Physical examination revealed only slight enlargement of the prostate and mild right flank tenderness. An excretory urogram showed right hydronephrosis and hydroureters due to lower ureteral obstruction. Blood chemistries were normal. Cystoscopy revealed a tumor of the trigone involving the right ureteral orifice. Under anesthesia, bimanual examination failed to disclose a mass in the bladder region and transurethral biopsy of the tumor was reported as mucus-secreting adenocarcinoma (fig. 3, *upper left*). Bone and chest roentgenograms were normal. An abdominal exploration was carried out 1 month after admission (August 21, 1957) and no evidence of metastases could be found, including biopsy of an iliac lymph node which was negative for carcinoma. Therefore, cystectomy and bilateral ureteroileocutaneous anastomosis (Bricker procedure) were performed. The pathologist reported the tumor to be superficial. On the 10th postoperative day, dehiscence of the wound and evisceration occurred. The wound was closed immediately in the operating room. The patient recovered and was discharged from the hospital 9 weeks after admission (September 27, 1957). An excretory urogram taken on November 14, 1957, revealed right calculous hydronephrosis. Bilateral ureteral reflux was found by ileogram on January 9, 1958, when he was readmitted because of uremia, dehydration and electrolyte imbalance. Blood chemistries were as follows: serum creatinine, 2 mg. per cent; chlorides, 107 mEq./L.; CO_2, 14 mEq/L.; and potassium, 4.2 mEq./L. At this time the excretory urogram revealed a nonfunctioning left kidney and right hydronephrosis. Surgical exploration on February 7, 1958, disclosed a left ureteral stricture at the level of the mesocolon. The redundant ileal segment was shortened by 20 cm. and the left ureter was reimplanted. The patient recovered and was able to return home.

Case 5. C. T. (WGH-34964), a 64-year-old white man, was first seen in 1952 because of gross hematuria and acute urinary retention. Cystitis and benign prostatic hypertrophy were diagnosed. He was followed for 3 years for recurrent hematuria. Pyelograms and several cystoscopies were normal. In 1953 a transurethral resection of the prostate revealed a diagnosis of adenocarcinoma. Radical perineal prostatectomy was subsequently performed as a curative procedure. In 1956 and 1957 he was cystoscoped several times because of urinary retention and hematuria. Finally, a bladder tumor was noted involving the left lateral wall in October 1957. This was resected transurethrally and the pathologist reported that it was a mucus-secreting adenocarcinoma of the bladder (fig. 3, *upper right*) and in no way resembled the adenocarcinoma of the prostate removed 2 years previously. The patient is being followed cystoscopically every 3 months.

Two instances of primary mucus-secreting adenocarcinoma of the colon mistaken for primary tumors of the bladder were seen recently and the following case reports illustrate the problems that were encountered in each.

Case 6. E. B. (UCH,LA 012-89-75), a 57-year-old white woman, developed dysuria and pyuria in February 1958 and was treated for cystitis. Response to antibiotics failed and she was seen by a urologist who performed cystoscopy and reported seeing a "malignant" bladder tumor. Subsequently, another urologist resected the discrete tumor, located upon the floor of the bladder in April 1958. The pathologist reported the specimen as showing cystitis glandularis (fig. 3, *lower left*). Follow-up cystoscopy 2½ months later revealed a more extensive bladder lesion and biopsy revealed mucus-secreting adenocarcinoma (fig. 3, *lower right*). Since this type of neoplasm could originate in the bowel, a barium enema was performed, although the history did not disclose bowel symptoms. The barium outlined an annular lesion of the sigmoid colon, typical of neoplasm. In June 1958 the sigmoid lesion and bladder were resected *en bloc*, colostomy was performed, and both ureters were implanted into a rectal bladder. She was alive and well without evidence of carcinoma 1 year after surgery.

Case 7. W. G. (HH-158998), a 68-year-old white man, was admitted to the hospital on April 26, 1958, for excision of a left hydrocele. He gave a history of having diabetes for 15 years and hematuria, dysuria and a low-grade fever for 6 weeks. Examination revealed hepatomegaly, abdominal fluid wave, pedal edema and cardiomegaly. Laboratory test results were: hemoglobin, 8.1 gm. per cent; blood-urea-nitrogen, 7 mg. per cent; Bromsulphalein retention, 31 per cent; serum bilirubin, 1.2 mg. per cent; 48-hour cephalin flocculation, 3 plus; mild left hydronephrosis depicted by excretory urography; normal gastrointestinal and colonic barium studies and bone roentgenography. Sig-

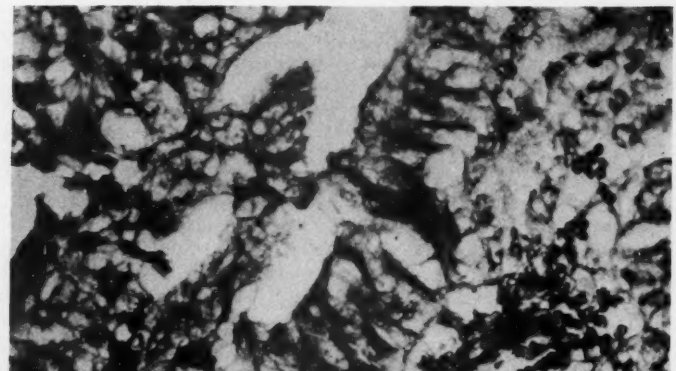

FIG. 4. Mucus-secreting adenocarcinoma in urinary bladder found to arise in large bowel (case 7).

moidoscopy was normal, but cystoscopy revealed a sessile, bleeding tumor on the dome of the bladder. The patient was given digitalis, diuretics and placed on a low sodium diet. This regimen improved his cardiovascular status. On the 18th hospital day bimanual palpation of the bladder under anesthesia did not reveal a mass or fixation. A biopsy of the bladder tumor was obtained transurethrally and the pathologist reported the diagnosis to be mucus-secreting adenocarcinoma (fig. 4). Rectal bleeding occurred 2 weeks later and again sigmoidoscopy was normal. However, a primary lesion of the colon was suspected and abdominal exploration on the 32nd hospital day disclosed a primary adenocarcinoma of the sigmoid colon which had invaded the bladder. The entire lesion including the bladder was resected *en bloc* and a colostomy was performed. A rectal bladder was created and the ureters were implanted into it.

DISCUSSION

Malignant tumors of the bladder may be classified as sarcoma and carcinoma. The latter are by far the more common (100:1). Of bladder carcinomas, 95 per cent are transitional cell, whereas the remaining 5 per cent are about equally divided between squamous cell and adenocarcinoma. Our particular interest in this report involves the 1 per cent of bladder malignancies that are mucus-secreting adenocarcinoma.

In 1924 Scholl[17] reported 5 cases of adenocarcinoma among 333 bladder malignancies (1.5 per cent). Ferrier and associates[6] reported a case of adenocarcinoma, as did Connel and Gnassi.[4] Lowry[14] described 5 cases of adenocarcinoma among 300 bladder tumors (1.6 per cent) and Ash[1, 2] reported 2 out of 2000 bladder

tumors in the Army Tumor Registry (0.1 per cent). Howard and Bergman[10] reported an instance of mucus-secreting adenocarcinoma, and in reviewing 1064 bladder tumors they found 8 adenocarcinomas (0.75 per cent; 2 mucus-secreting). Franksson[7] reported 334 bladder tumors of which 13 were adenocarcinomas (12 urachal in origin); 8 were mucoid in nature. Signet-ring cell tumors are the anaplastic counterpart of mucus-secreting adenocarcinomas. Only 2 cases had been presented in the literature by 1954; Lowbeer[13] encountered another case in 1955, and we are reporting 1.

The exact explanation of the origin of adenocarcinoma in the transitional cell-lined bladder is not known. However, glandular structures are frequently present in the subtrigonal, subcervical and urachal areas. These sites are the more frequent locations of adenocarcinoma. Chronic irritation and infection give rise to metaplastic changes. These are frequently seen as cystitis cystica and glandularis. The latter is commonly held to be precancerous.[18] Adenocarcinoma is not an uncommon complication of untreated extrophy of the bladder in the adult. Another theory is that intestinal gland rests are found in the bladder, related to its origin from the cloaca. Thus, adenocarcinoma may arise anywhere in the bladder.

The diagnosis is made primarily by endoscopic examination and biopsy of the bladder lesion. Its origin in the bladder is confirmed through exclusion of a primary lesion in the gastrointestinal tract. This assumes that roentgenograms of the stomach, small intestine and large bowel are normal. Cystography, excretory urography and roentgenography of the chest and selected bones add to the evaluation of the extent of the lesion. The primary site is particularly difficult to determine when a fistula connects bowel and bladder. In all of our cases the diagnosis was made by transurethral biopsy. However, the differentiation from one arising in the gastrointestinal tract was not easy. This question could be resolved only through autopsy in case 3.

The treatment is the same as that used for other bladder tumors. Transurethral resection may suffice for early or superficial tumors. Partial, or more often, total cystectomy may be necessary for those lesions invading the muscularis or involving the ureteral orifices. Irradiation may be used if the patient does not desire surgery. Of our 3 patients submitting to total cystectomy with the hope of being cured 2 died of carcinomatosis. However, the 1 living patient has enjoyed a 10-year survival to date. Thus, the prognosis of this type of tumor is not hopeless.

The prognosis is also the same as that for other bladder carcinomas. Results of surgery are inversely proportional to the extent of the tumor. A high percentage of cures may be anticipated for the adequately treated, early, superficial tumors. Extensive tumor invasion offers a grim outlook.

SUMMARY

Five case reports of an uncommon urinary bladder tumor, mucus-secreting adenocarcinoma, have been presented. Three cases were at first thought to be prostatic or rectal in origin, but the correct diagnosis was ascertained at the time of cystectomy in two and at autopsy in the third. The treatment and prognosis is the same as for other bladder neoplasia.

Dr. Chester C. Winter
University of California Medical Center
Los Angeles 24, California

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SENILE OSTEOPOROSIS AS A DISORDER INFLUENCING TREATMENT AND END RESULTS OF FRACTURES OF THE HIP: WITH A PRELIMINARY REPORT ON THE USE OF COLLAPATITE*

MARSHALL R. URIST, M.D., ROBERT MAZET, JR., M.D., AND CHARLES O. BECHTOL, M.D.

Los Angeles, California

A high percentage of the poor results of fracture of the hip can be attributed to postmenopausal or senile osteoporosis. The importance of this disorder as a factor influencing the incidence, choice of treatment, complications, or nonunion requires special consideration. Osteoporotic bones tolerate metal very poorly. Collapatite, a derivative of bone, will be introduced in this report, as a substitute for metal for internal fixation of osteoporotic hips in an attempt to find a solution to the serious problem of the subcapital fracture.

MATERIALS AND METHODS

During the period from 1948 to 1953, 24 patients admitted to the four local hospitals for fractures of the hip were found to have had previous x-ray examinations of the spine and treatment for severe osteoporosis During the period from 1953 to 1959, special x-ray examination of 100 consecutive women with hip fractures revealed 76 additional cases of osteoporosis. These 100 patients with fracture of the hip associated with osteoporosis of the spine were treated by various methods as shown in table 1; 51 patients had intertrochanteric fractures and 49 patients had intracapsular fractures. The intracapsular fractures were classified as shown in table 2.

The complications of treatment were analyzed and tabulated in 100 cases (table 3). The end result examinations were made in 30 patients who lived for 2 years after a subcapital fracture (table 4); 19 or 39 per cent died of various nonsurgical causes. Lateral views of the spine were also prepared in 25 selected cases of subcapital fractures with poor end results due to nonunion or avascular necrosis or both in the head of the femur (table 5).

Ten additional recent cases were treated with pegs made of a derivative of bone (Collapatite) in an effort to find a material that patients with

TABLE 1

Treatment of 100 fractures in osteoporotic patients

Treatment	Number
Intracapsular fractures	
Smith-Petersen nail	31
Thompson Z nail	9
Neufeld nail	4
Badgley nail	1
Prosthesis, Moore	3
Prosthesis, Thompson	1
Total	49
Intertrochanteric fractures	
Neufeld nail	37
Smith-Petersen nail, Thornton plate	11
Jewett nail-plate	2
Prosthesis	1
Total	51

TABLE 2

Classification of 49 intracapsular fractures of hip joint

Classification	Number	Per Cent
Unstable, adduction, displaced	39	80
Intermediate, undisplaced	8	16
Stable, abduction, valgus	2	4
Total	49	100

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* From the Division of Orthopedics, Department of Surgery, University of California Medical Center, Los Angeles 24, California, and Wadsworth Hospital, U. S. Veterans Administration Medical Center, Sawtelle, Los Angeles 25, California.

TABLE 3

Mechanical complications in 100 fractured hips in osteoporotic patients

Complication	Per Cent
Retrograde migration of nail	12
Perforation of joint by nail	30
Fatigue fracture of nail-plates	4
Drifting or loose prosthesis	4
None	50
Total	100

TABLE 4

Follow-up on 49 intracapsular fractures of hip with senile osteoporosis

Result	Number
Survivors after 2 years (30 patients)	
Nonunion	14
Union	14
Prosthesis, *per primam*	2

subcapital fractures associated with osteoporosis might tolerate better than metal (table 6).

Biopsy examinations were made of the lateral cortex of the femur 6.0 cm. distal to the externus tubercle of the greater trochanter just distal to the insertion of a bone peg in 10 normal women and 24 women with severe osteoporosis of the spine. The specimens were sectioned undecalcified on a bone mill, 100 μ in thickness and examined by microradiography.

Radiologic and histophysiologic features of osteoporosis. The diagnosis of osteoporosis in the cases presented in this report was based upon three or all of the following objective findings: (1) collapsed vertebra in the dorsal spine, (2) expanded intervertebral discs in the lumbar spine, (3) bones with a thin cortex in bone of the above areas of the spine, (4) accentuation of the vertical trabecular markings in the interior of the vertebral bodies and the head of the femur due to preferential absorption of the horizontal trabeculae (fig. 1).

The alterations in the microradiographic

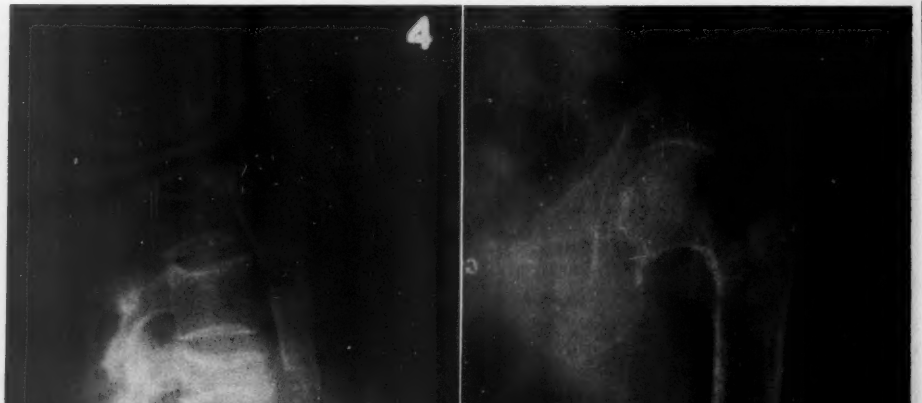

FIG. 1. *A*, lateral view of the lumbar spine showing calcification of the aorta, collapse of the 1st and 4th lumbar vertebrae, "ballooning" of the discs, and thinning of the cortex of the bones in the case of a 76-year-old woman with a fracture of the hip. *B*, roentgenogram of the hip in the view of the same case as shown in figure 1*A*, after a fracture of the neck of the femur, caused merely by the patient's turning over in bed one night. Note the thinning and longitudinal striations of the cortical bone of the shaft of the femur.

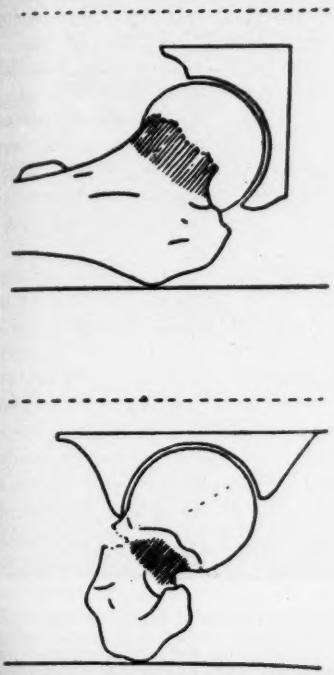

FIG. 2. Diagrams showing area of the neck of the femur commonly lost by resorption and spontaneous fracture. Patients with osteoporosis of the spine lack sufficient thickness of cortical bone in the posterior wall of the femoral neck to withstand trivial injury. The bone splinters in the area demarcated by the shading. The fracture angulates anteriorly and it is often impossible to reduce it because of absence of bone substance. Anteroposterior view (*above*) and lateral view (*below*). (From Linton.[5])

structure of the cortical bone were considered pathognomonic of osteoporosis. The thickness of the cortex of the lateral aspect of the femur 3.0 cm. distal to the externus tubercle was only 30 per cent of the thickness of the cortex of non-osteoporotic individuals. On the endosteal surface of the cortex the vascular channels were greatly enlarged. Assuming that lamellae of low radiodensity are lamellae of new bone, it was surprising to note that there was more new bone formation in the osteoporotic than the non-osteoporotic cortex. Some of the haversian canals were plugged up with calcium deposits. Histologic sections, however, showed almost no evidence of osteoclasts. In general, the over-all microscopic picture suggested that osteoporosis is probably due to a disturbance of the process of remodeling of new haversian systems. The humoral factors controlling this process are not known, and the cause of either postmenopausal or senile osteoporosis is still quite obscure. The medical studies performed on the patients described in this report were summarized in a previous communication[9, 10] (figs. 2 and 3).

RESULTS

Fractures occurred in the proximal end of the femur at various levels in patients with osteoporosis. Although there was a history of only trivial injury or no injury, there was no apparent site of predilection for the fracture. However, it was apparent that in the majority of cases, the fractures were more comminuted than generally seen in nonosteoporotic individuals. The intertrochanteric region was often highly rarified, fragmented, and very brittle. The femoral neck consisted of only a thin shell of bone. The subcapital fractures were almost invariably spiral fractures with splintering of the posterior cortex. No special consideration for osteoporosis was given in the choice of treatment of these fractures. The attending and house surgeons employed metallic internal fixation or a prosthesis in every case as shown in table 1.

Intracapsular fractures. The high degree of comminution of the fracture occurring in osteoporotic hips resulted in an extraordinarily large number of patients with displaced or unstable adduction type as shown in table 2. Two patients with intermediate or undisplaced fractures were erroneously treated by bed rest and splints, before the fragments came apart. In these cases, the fractures were converted into the adduction or varus type.

Complications. Mechanical failure, as might have been anticipated, occurred in exactly one-half of the cases. The design of the appliance appeared to have no bearing on its efficiency in transfixing brittle bone. As illustrated in table 3, when a nail was used to transfix the femoral neck, the splintered cortical bone was absorbed, and the metal was extruded backward in 12 instances. When a nail-plate was used for internal fixation of intertrochanteric fractures, the dissolution of the splintered cortex resulted in migration of the end of the nail into the joint. In 4 patients with intertrochanteric fractures the metal appliances broke before union could occur. In 4 of the 5 cases in which a prosthesis was used, the metallic femoral head either drifted through the thin articular cortex of the acetabulum or

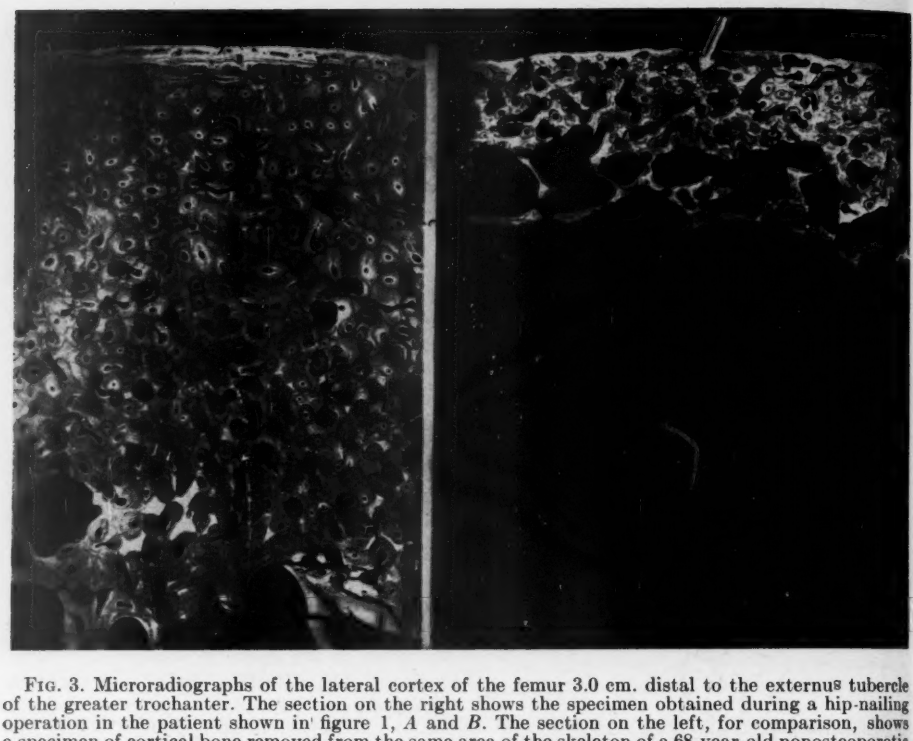

FIG. 3. Microradiographs of the lateral cortex of the femur 3.0 cm. distal to the externus tubercle of the greater trochanter. The section on the right shows the specimen obtained during a hip-nailing operation in the patient shown in figure 1, *A* and *B*. The section on the left, for comparison, shows a specimen of cortical bone removed from the same area of the skeleton of a 68-year-old nonosteoporotic individual. Osteoporosis caused loss of two-thirds of the normal thickness of the cortex, enlargement of the haversian canals, many lamellae of new bone with low density calcification, and a bizarre shaped network of old bone on the endosteal surfaces of the femur. Many of the haversian canals situated in the deeper areas of the cortex (marked by the *arrow*) were plugged up with deposits of calcium. (Reprinted with the permission of Blakiston & Sons.)

TABLE 5

Findings in 25 consecutive subcapital fractures with poor end results of nailing operations

Finding	Number	Per Cent
1. History of trivial injury	21	84
2. Nail protruding into acetabulum	11	44
3. Retromigration of nail from neck	9	36
4. Absorption of neck	22	88
5. External rotation contracture	25	100
6. Avascular necrosis of head	1	4
7. Fracture reduced and nail well placed	12	48
8. Fracture not reduced or imperfect nailing	13	52
9. Compression fractures, osteoporosis of dorsal spine	21	84
10. Codfish vertebra, lumbar spine	15	60
11. Compression fractures, lumbar spine	10	40
12. All changes (9 + 10 + 11)	9	36

TABLE 6

Fractures of neck of femur treated by internal fixation with Collapatite peg

Case No.	Age	Type of Fracture	Source*	Date of Operation	Date of Union
1	82	Basal neck	B	10/ 1/58	4/23/59
2	74	Subcapital	B	10/ 3/58	5/30/59
3	94	Subcapital	B	12/ 5/58	Myocardial failure, 1/10/59
4	91	Subcapital	B	12/ 7/58	Died, 1/12/59
5	68	Basal neck	B	1/ 2/59	5/15/59
6	70	Subcapital	B	1/ 2/59	Healing well
7	74	Subcapital	H	2/20/59	Healing well
8	79	Subcapital	H	3/16/59	Healing well
9	80	Subcapital	H	3/24/59	Died of carcinomatosis, 4/1/59
10	64	Subcapital	B	5/28/59	Healing

* B = bovine; H = human.

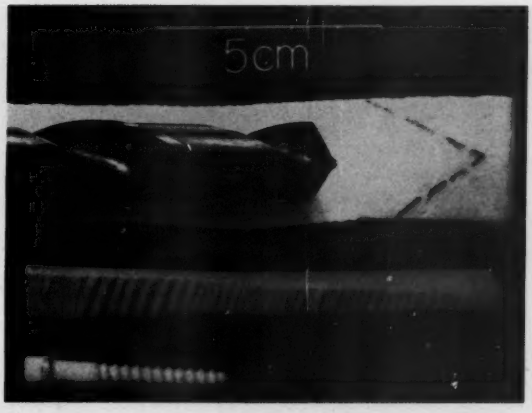

FIG. 4. Photograph showing 1.5-cm. drill point and 2.0-cm. strip of bovine Collapatite (*top*); another strip turned on its side to show the thickness (*center*), and a screw that was machined from Collapatite (*bottom*).

became so loose around the stem that there was painful piston action of the prosthesis inside the marrow cavity of the femur.

End results. The end results of the intertrochanteric fractures in osteoporotic individuals appeared to be the same as reported in unselected series of cases consisting of both nonosteoporotic and osteoporotic patients. The end results in 49 intracapsular fractures were of special interest because 19 patients failed to survive the injury for 2 years and of the remaining 30 cases more than one-half had nonunion or a femoral head prosthesis (table 4). In unselected cases the average incidence of nonunion has been reported to be approximately 30 per cent in the hands of skilled surgeons.

An even more impressive view of the deleterious role of osteoporosis in the poor results of fracture of the hip are the findings in a spine survey in 25 consecutive cases of nonunion in subcapital fractures treated by 11 surgeons in two large hospitals (table 5). Approximately 84 per cent had collapsed vertebra and severe osteoporosis of the spine preceding and associated with the fracture of the hip.

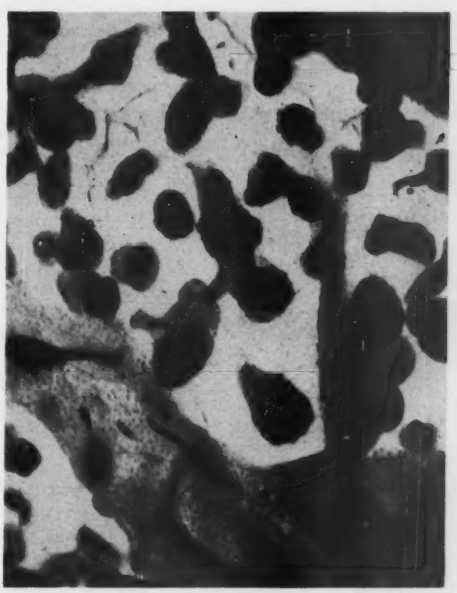

FIG. 5. Collapatite was produced from calf bone. Three months after implantation in the upper end of the tibia of a dog, the new bone produced by the host contains osteocytes and has low radiodensity. The Collapatite contains no cells and has the same high radiodensity as the original bovine tissue.

FEMORAL NECK FRACTURES TREATED WITH A COLLAPATITE PEG

In table 6 are listed 10 patients who were treated with an intramedullary peg of Collapatite. Collapatite consists of a derivative of human or calf bone, excised sterile at autopsies at the United States Naval Hospital, Bethesda, Maryland, Tissue Bank, or at the Animal Processing Plant of Squibb Institute for Medical Research. The sterile cortical bone was cut in strips, 10.0 to 12.0 cm. in length, 2.0 to 2.5 cm

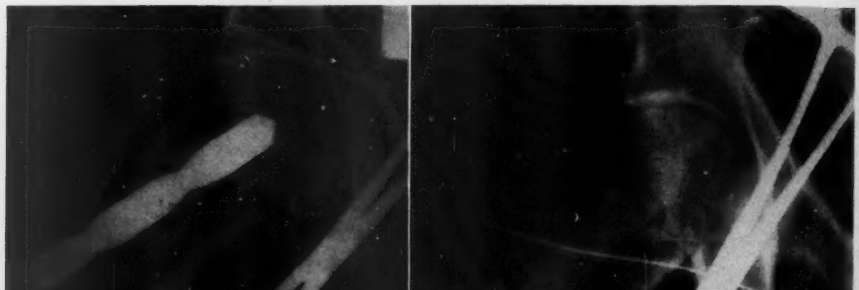

FIG. 6. *A*, roentgenogram of a subcapital fracture in the anteroposterior view, showing drill point in the center of the head. *B*, roentgenogram of a subcapital fracture in the anteroposterior view, transfixed with a Collapatite peg made from the crest of the tibia removed from an autopsy subject under sterile conditions.

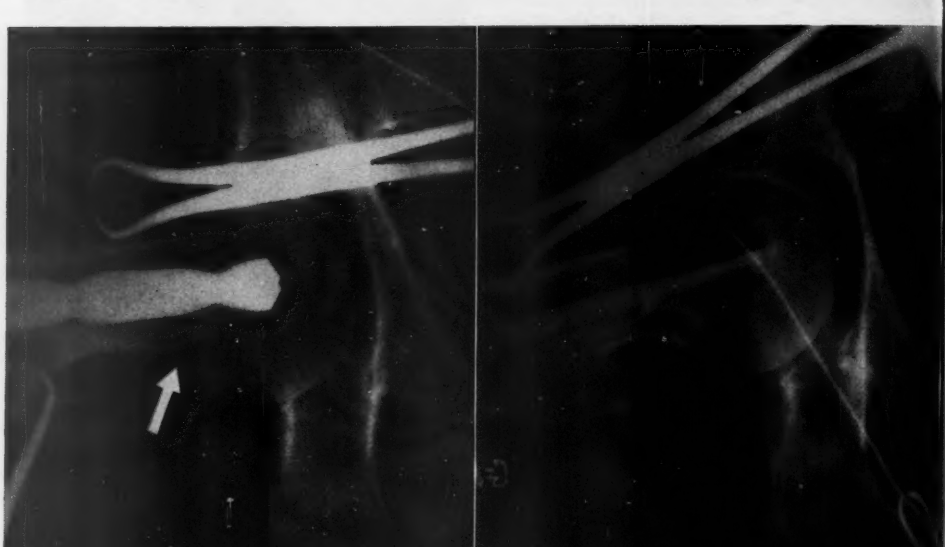

FIG. 6. *C*, roentgenogram of the fracture shown in the lateral view of figure 6, *A* and *B*, showing the fracture reduced, the drill point in place, and the splintered posterior cortex (indicated by the *arrow*). *D*, roentgenogram in the lateral view of the fracture shown in figure 6, *A* to *C*, with the Collapatite peg in place, and the fragments of the posterior aspect of the neck of the femur in place.

in width, and full thickness of the cortex, with the aid of an electric motor saw, and lyophilized for preservation and reduction of the antigenic properties of the tissue. Collapatite was prepared from these strips as follows: (1) immersion in 8 per cent solution of urea for 24 hours to increase the permeability of cell membranes; (2) immersion in a dilute solution of chymotrypsin for 24

hours to dissolve noncollagenous proteins. (3) immersion in 8.8 per cent saline and agitation on a shaking machine for three 24-hour periods to remove noncollagenous protein; (4) immersion in petroleum ether for 24 hours to remove fats; and (5) autoclaved for 10 hours at 15 pounds pressure, and sealed in a sterile container for storage.*

Collapatite prepared from cortical bone as described above had the tensile strength, and bending and torsion resistance of oak wood. It was not as strong as steel, but when used as a massive rectangular shaped peg in the interior of the femoral neck it was sufficiently strong to hold the fracture until healing was complete. The fragments that were held together in an osteoporotic hip were so much more brittle than Collapatite, that the peg did not need to be as strong as steel. Collapatite was very slowly absorbable and well tolerated by the tissues. Experiments with this material as compared with various other materials implanted in the head of the tibia of rabbits for 3 years will be reported in another communication. Similar to the beef bone pegs, screws, and plates, the residue of a Collapatite peg probably will remain in the bone for many years.

The surgical procedure for insertion of a Collapatite peg is the same as employed for the Smith-Petersen trifin nail (figs. 4 to 6).

DISCUSSION

Space does not permit a review of the large literature on fracture of the hip. In over 200 articles published in English, French, and German languages during the past 25 years, postmenopausal or senile osteoporosis has been mentioned by only 11 writers, and in not one of these instances has any effort been made to treat patients with this disorder with special precautions or methods. Linton,[5] Gray[3] and Scheck[7] emphasized the poor prognosis in patients with comminuted fractures but did not associate this type of hip injury with osteoporosis. Ghormley,[2] however, described osteoporosis as a contraindication to the use of a hip prosthesis.

The foregoing observations suggest that comminuted femoral neck fractures are common in osteoporosis, that metal is poorly tolerated by osteoporotic bones, and that, if it is at all possible, surgical implantation of metal appliances should be avoided. The effort to substitute biologic materials for metal is not new. Albee and Preston[1] recommended autogenous massive grafts of the fibula in hip nailing operations. Watson-Jones[11] found that this was not strong enough to be relied upon for internal fixation and recommended the method of King,[4] who perfected a trifin-nail-fibular transplant operation.

Availability and absence of physical strain on the patient are probably responsible, to a considerable measure, for current preference for metal for internal fixation of fractures. It is not necessary, however, to use metal, and a derivative of bone such as Collapatite can be made and stored in any hospital for use in patients with osteoporosis. Orell[6] prepared a similar material, os purum, by cleaning calf bone and soaking it in salt solution and warm potassium hydroxide to remove proteins, and then in acetone to remove fat. Orell and many others who followed him made the mistake of employing os purum as if it were a substitute for a bone graft, and its use gradually fell into disrepute in many clinics. Collapatite is essentially the same material as os purum, except that it is generally prepared from lyophilized human autopsy bone (but can be made from animal bone) by new and improved methods of extracting noncollagenous proteins and other antigens. But most important, it is necessary to emphasize that Collapatite is not bone but a derivative of bone; it should never be used for a bone graft but only as a substitute for metal. It is superior to metal because it is not encapsulated in fibrous tissue and the host is able to attach it to the skeleton by the formation of cement substance.[8]

Collapatite, like other processed proteinaceous material, such as catgut or silk thread, appears to be relatively free of risk. Beef bone plates, screws, nails, and pegs were employed without chemical extraction of antigenic proteins and many favorable and few unfavorable results were reported in the era before the advent of metal alloys. By special processing such as em-

*Since this manuscript was submitted for publication the process of extraction has been changed in sequence, chymotrypsin has been omitted, and autoclaving has been replaced by cold sterilization as follow: (1) acetone for 24 hours, (2) 8 per cent urea for 24 hours, (3) 8.8 per cent saline and agitation or a shaking machine for 24 hours, (4) 1 per cent β-propriolactone, in a $NaCl \cdot NaHCO_3$ buffer at 4°C. for 48 hours for sterilization, (5) wash in distilled water for 24 hours, and (6) storage in sterile vials after drying in an oven.

ployed in the production of Collapatite, biologic materials may be made more useful for internal fixation of fractures in the future.

SUMMARY

1. Preoperative lateral view roentgenograms of the dorsal and lumbar spine should be examined in every case of fracture of the hip. Patients showing collapsed vertebrae in the dorsal spine, "ballooned" intervertebral discs in the lumbar spine, thin cortex on the vertebral bodies throughout the spine, and other gross evidence of postmenopausal or senile osteoporosis should be given surgical treatment only with great caution.

2. Patients with fractures of the hip associated with osteoporosis do not tolerate metal and can develop serious complications in at least 50 per cent of the cases.

3. Collapatite, a derivative of bone, was used in place of metal in 10 osteoporotic patients in an attempt to improve the generally poor end results of subcapital fractures. The end results observed in the first 3 cases were excellent; a larger number of patients, however, must be observed for at least 2 years after the operation; further investigations are in progress to determine the protein and water content as well as the weight and shape of the Collapatite peg necessary to meet the exact mechanical requirements for internal fixation of the femoral neck.

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Dr. Marshall R. Urist
University of California Medical Center
Los Angeles 24, California

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ACUTE CHOLECYSTITIS*

JOHN D. BRIGGS, M.D., PHILIP G. BEAL, M.D., AND G. ARNOLD STEVENS, M.D.

Los Angeles, California

Although the first cholecystectomy for acute cholecystitis was performed nearly a half century ago, there are few records of operations for this disease before 1930. During the ensuing decade there was increasing interest in the application of early operative procedures,[5] either cholecystectomy or cholecystostomy. Most American surgeons believe that acute cholecystitis should be treated by cholecystectomy. There is not, however, a unanimity of opinion as to the time in the course of the disease that cholecystectomy should be carried out. Many surgeons have recognized that because of local acute inflammatory reaction, identification of important structures is sometimes more difficult than in the chronic stage of cholecystitis. To add to the surgeon's difficulties when cholecystectomy is undertaken as an emergency procedure, there may be inadequate anesthesia, unskilled assistance and sometimes improper illumination of the operative field. Because of the many difficulties listed above, the trend in surgical thinking in the past few years, as portrayed in the medical literature, has been more in favor of delaying surgery until the acute stage has passed.

However, at Wadsworth Hospital all patients in whom the diagnosis of acute cholecystitis was made, during the 6 years subsequent to 1950, were operated upon as soon as fluid and electrolyte deficiencies were corrected. The operation was performed without regard to the time elapsed since onset of symptoms. This report is based upon experience gained in the management of 141 patients treated in this manner.

Acute cholecystitis is defined as that condition manifested clinically by pain, tenderness and spasm in the right upper quadrant of the abdomen and often by a palpable mass, the result of an acutely inflamed, enlarged gall bladder. The operative findings in each instance confirmed the diagnosis of acute cholecystitis. All gall bladders included in this study were examined histologically and reported by the pathologist as showing acute or subacute inflammatory changes, consistent with a clinical diagnosis of acute cholecystitis.

* From the Surgical Service, Wadsworth Veterans Administration Hospital and the Surgical Department, University of California Medical Center, Los Angeles, California.

CLINICAL STUDY

The patients in this series range in age from 24 to 89 years with the great majority falling in the 6th and 7th decades. This corresponds with the age at which chronic cholecystitis is most frequently found. Only 3 of the patients were women and a similar number were Negro. All of the 141 patients had pain of more or less severity in the right upper quadrant of the abdomen; 116 were nauseated and in 102 this was of sufficient degree to cause vomiting. Fatty food intolerance was mentioned by 67 patients and 64 gave a history of one or more previous episodes of right upper quadrant pain, indicating that in a considerable number disease of the gall bladder had been present for many years. In 9 patients, jaundice was present before the onset of the acute episode.

Symptoms of acute cholecystitis had been present in 41 patients for less than 24 hours; 55 had been ill 2 to 3 days, and 31 up to 1 week. Thirteen had symptoms from 7 to 42 days, indicating that acute cholecystitis may sometimes be a prolonged process.

Hays and Glenn[7] stated that cholecystostomy is quite frequently followed by redevelopment of calculi and further episodes of acute cholecystitis. Two of our patients had had a prior cholecystostomy and a third had drainage of the gall bladder on two occasions with reformation of calculi.

As had been pointed out by Glenn,[6] the onset of acute cholecystitis sometimes occurs following unrelated disease. The acute episode leading to operation in 5 patients of this study followed surgery; in one instance each, for brain abscess, pneumonectomy, gastric resection, transurethral resection and appendectomy.

Since it has been shown that bacterial infection seldom occurs early in the course of acute cholecystitis,[12] febrile reaction should not be a prominent feature of the clinical syndrome; 61 of our patients had a temperature of 99° or less and an additional 41 had fever of less than 100°. Only 1 patient had fever of over 103°. All patients had tenderness in the right upper quadrant of the abdomen with associated spasm and rebound tenderness. A mass believed to be the gall bladder was palpable in 67. In 17 patients serum bilirubin levels were increased sufficiently to cause clinical jaundice.

The white blood count was elevated more frequently than the temperature. Only 25 patients had a leukocyte count below 10,000; 93 had a count between 10,000 and 20,000; and 19 a count of over 20,000. The highest white count, 40,000, was in a patient who had been ill for 3 days. Of the 104 patients who had serum amylase determinations, 91 had normal values of less than 200 units; 9 had a level between 200 and 500; and 4, over 500 units. Abdominal roentgenograms were taken frequently, but shadows believed to be stones in the gall bladder were seen in only 12 patients.

Fluid and electrolyte imbalances were corrected before the patients were operated upon. Antibiotics were given frequently, particularly to those who had elevated temperature and leukocyte counts. Gastric suction with a Levin tube was employed in most instances to minimize the hazard of pulmonary aspiration. Operation was undertaken within 3 hours following admission to the hospital for 26 patients; 4 to 6 hours for 36, and under 12 hours for an additional 19. A longer period of hospitalization before surgery in the remaining patients was due largely to indecision as to the correct diagnosis. Recently, more frequent use of the intravenous gall bladder dye study has caused such delay to be seldom necessary.

Operation was performed through a subcostal or right rectus incision and the gall bladder was frequently removed from fundus downward. The cystic artery and duct were separately isolated and ligated after identification of the common and hepatic ducts. Cholecystostomy with evacuation of the contents of the gall bladder and insertion of a drainage catheter was done in 8 patients. Of the 133 who underwent cholecystectomy, 17 had exploration of the common duct.

TABLE 1

Complications

Wound	9
Pulmonary	8
Vascular	8
Fever	4
Serum hepatitis	2
Draining sinus tract	2
Injury to common duct	1
Cystic duct remnant	1
Septicemia	1
Postoperative hemorrhage	1
Urinary retention	1

An acute edematous or hemorrhagic gall bladder was found in each case in this series. Of the 36 patients who had gangrenous changes of the gall bladder wall, 10 had localized perforations with abscess and 5 had free perforation with generalized peritonitis. Calculi were found in the gall bladder of 132 patients and 9 did not have stones. Cholodocholithiasis was present in 11 of the 17 common ducts that were explored. Several patients with jaundice did not have exploration of their common duct, the surgeon believing that the icterus resulted from inflammatory changes about the duct.

In table 1 are listed 38 complications which occurred in 31 patients. Two complications were due to technical errors. One patient had a cystic duct remnant of sufficient length that a stone reformed, requiring later removal. A 2nd patient had a portion of his common duct removed. This was corrected on the 5th postoperative day by cholodochojejunal anastomosis. This patient has had no further trouble during the 3 years that have elapsed since operation. Of 9 complications related to the abdominal wound, 8 were due to infection and the other to wound separation. One patient with wound infection died from septicemia. Three patients had lowered blood pressure to shock levels in the immediate postoperative period. All responded to appropriate therapy. The other cardiovascular complications included 2 instances of phlebitis; 2 of cardiac decompensation, 1 resulting in death of the patient; and a renal shutdown also leading to the patient's death. Three pulmonary complications were serious. Two occurred in a patient who had a pulmonary embolus from an area of phlebitis in his leg and who subsequently developed a bronchopleural fistula. Another patient died from pneumonia.

TABLE 2

Summary of deaths

	Age	Duration of Symptoms	Other Disease	Complication	Surgical Procedure	Cause of Death
		days				
1	73	8	Arteriosclerotic heart disease	Gangrene of gall bladder	Cholecystectomy	Uremia
2	76	10	Myocardial infarction	Perforation of gall bladder and peritonitis	Cholecystectomy, exploration of common duct	Acute pulmonary edema
3	64	5	5th postop. day for pneumonectomy	Gangrene of gall bladder	Cholecystostomy	Cardiac failure
4	75	1	Carcinoma of the colon	Hemorrhagic cholecystitis	Cholecystectomy	Pneumonia
5	69	7	6 weeks postop. for gastric resection	Hemorrhagic cholecystitis	Cholecystectomy	Wound infection septicemia

Five patients died following gall bladder surgery (table 2) before discharge from the hospital, a mortality rate of 3.5 per cent. The 1st death occurred in a 73-year-old patient with severe arteriosclerotic heart disease, for which he had been hospitalized a few weeks before readmission for removal of a gangrenous gall bladder. He had symptoms of pain and tenderness in the right upper quadrant for 8 days and cholecystitis was suspected by his physician for the latter 3 days. At the time of surgery, on the 8th day of his disease, cardiac massage was necessary to restore circulation. He developed a wound separation, renal shutdown, and succumbed from uremia on the 22nd postoperative day. The outcome in this patient might have been different if surgery had not been delayed for several days after the diagnosis of acute cholecystitis had been made.

The 2nd death was a 76-year-old man with a history of two episodes of myocardial infarction. He was operated upon 24 hours after admission because of a diagnosis of acute cholecystitis of 10 days' duration. His temperature was 98.6; white blood count, 6400; and a mass was palpable in the gall bladder area. He did not appear to be acutely ill but his condition deteriorated following admission. At operation he was found to have a free perforation of the gall bladder and a generalized peritonitis. Because of a mild icterus the surgeon elected to explore the common duct in addition to removing the gall bladder, a procedure that required several hours. The patient died of acute pulmonary congestion on the 5th postoperative day. From this vantage point, either cholecystostomy or cholecystectomy without exploration of the common duct would seem to have been a wiser procedure in this acutely ill patient.

A 3rd patient died 5 days after cholecystostomy was performed under local anesthesia for gangrenous cholecystitis developing in the postoperative period following pneumonectomy for carcinoma of the lung. Symptoms of acute cholecystitis occurred 3 days after the pneumonectomy, but surgery for it was delayed 2 days.

A 75-year-old man died from pneumonia after being transferred to the Medical Service, 20 days following cholecystectomy for acute hemorrhagic cholecystitis. He had been ill 1 day before his operation and had apparently recovered from the effects of the surgery. At autopsy he was found to have carcinoma of the colon.

A 5th patient also had cholecystectomy for acute hemorrhagic cholecystitis, 24 hours after admission and 7 days after the onset of symptoms. Re-exploration was necessary for bleeding in the omentum and he developed a severe wound infection. Death occurred on the 114th postoperative day from septicemia secondary to the wound infection.

The operations reported in this series were performed by many surgeons, most of whom were surgical residents. No one individual performed more than five or six procedures. Operative times were longer and complications more frequent than are found in those series reflecting the work of a single or of a few surgeons. However, the mortality rate compares quite favorably with most reports. One and possibly 2 deaths might have

been avoided if the patient had been referred to the surgeon more promptly. A prolonged, unwise procedure was chosen in one instance for which the surgeon must accept responsibility for the unfavorable outcome. All 5 deaths occurred in patients over 60 years of age.

The injury to the common duct was most unfortunate. However, the patient has been without further symptoms following the one reconstructive procedure. The cholecystectomy in this patient was accomplished without particular difficulty, injury to the duct being due to haste and insufficient identification of important structures. The remnant of cystic duct was left behind because of difficulty in following it to its junction with the common duct. Retrograde dissection may in some instances facilitate identification of these structures.

DISCUSSION

This study indicates that the disease failed to regress in many patients with acute cholecystitis, or that further episodes occurred before subsidence had taken place. Operative procedures often became more difficult when performed at a later date. There was also difficulty, as has been repeatedly pointed out,[1] in determining when progression of the pathology was occurring with development of serious complications. For these reasons, the policy was adopted to operate upon all patients in whom the diagnosis was reasonably well established, after a short period of preoperative preparation, regardless of the day of their disease.

The course of acute cholecystitis is in many respects similar to that of acute appendicitis. Initially in each disease, relatively minor constitutional changes are found, since the primary etiologic factor is due to obstruction of the organ. There follows a period of 2 to 3 days in which the process remains localized. In 15 to 20 per cent of patients with appendicitis and acute cholecystitis perforation and abscess formation will develop, due to gangrenous changes in the wall. The pathologic changes in the remaining patients undergo resolution and subsidence of the inflammatory process.

One of the objections raised to those who advocate early operation for acute cholecystitis is that the diagnosis may be in doubt. In some instances this objection is valid and surgery was delayed in many of our patients because of diagnostic uncertainty. Intravenous cholangiocholecystography as advocated by Jordan[9] and Johnson and associates[8] is of assistance in excluding other pathologic entities that are manifested by pain and tenderness in the right upper quadrant. This study can be performed in a few hours, while fluid and electrolyte deficiences are being corrected, and will lead to a lowered incidence of diagnostic error.

One surgeon,[10] who advocates that all patients with acute cholecystitis be treated by watchful waiting, avoiding surgery whenever possible, complains that the average surgeon rarely sees these patients in less than 48 to 72 hours after the onset of symptoms. This will become increasingly true if this policy is followed. As was formerly the case of patients who had appendicitis, only those who have developed a complication will find their way to the surgeon. Barksdale and Johnson[1] state "One of the greatest arguments against conservative therapy is that its practice by surgeons has led to widespread observation of acute cholecystitis by general practitioners and medical men."

Many patients who have died following surgery for acute cholecystitis were observed for several days in the hospital until it became obvious that there was progression of the disease.[3] The outcome for some of these might have been different had they received early surgery. Ross and associates[11] have mentioned that avoidance of surgery during any particular given time does not decrease, but may increase the technical difficulties of operation, while increasing the morbidity of the disease. The increased mortality that occurs in the 4- to 12-day period is a result of the disease process and not whether surgery is performed or withheld during that period.

SUMMARY

The clinical course of 141 patients with acute cholecystitis who were operated upon as soon as fluid and electrolyte deficiences had been corrected, without relation to the time of their disease, has been presented. There were 5 deaths in this series, all in patients over 60 years of age, a mortality rate of 3.5 per cent. Cholecystostomy was performed in 8, or 5.7 per cent, and the remaining 133 patients received definitive treatment by cholecystectomy. A study of these

patients does not lead us to desire to change our present plan of therapy.

Dr. John D. Briggs
University of California Medical Center
Los Angeles 24, California

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ANTIBODY RESPONSE TO HOMOGRAFTS. II. PRELIMINARY STUDIES OF THE TIME OF APPEARANCE OF LYMPHOAGGLUTININS UPON HOMOGRAFTING*

PAUL I. TERASAKI, PH.D.†

Los Angeles, California

Although a great deal of evidence indicates that serum antibodies do not play a role in the rejection of homografts,[1, 7, 13, 16] in the past few years some evidence has been brought forward demonstrating successful passive transfer of immunity to homografts by serum.[4, 17] Recently, Harris and associates[8] reported the destruction of homologous lymph node cells *in vivo* by the sera of animals injected with leukocytes from the lymph node donor. An *in vitro* test for the detection of antibodies directed against homologous tissue was described by Terasaki and associates.[19] With this method, lymphocytes from the homograft donor were agglutinated by serum from the homograft recipient. The present paper shows the time at which sera of homografted animals acquire the ability to agglutinate lymphocytes. Preliminary results reported here indicate that the time of appearance of lymphoagglutinating ability of the sera is consistent with the idea that lymphoagglutination is caused by antibodies. These "antibodies" do not appear in the blood until after the destruction of skin homografts.

METHODS

Three White Leghorn (WL) adult chickens were grafted with a 4- by 5-cm. piece of skin from adult New Hampshire (NH) chickens. The grafts were sutured on the backs and painted with collodion. Four-day-old chicks were grafted with skin from other 4-day-old chicks of the same breed (WL or NH). For comparisons with the adult chickens, only the tests of sera of 6 chicks which sloughed their skin homografts within 2 weeks are reported here. One chick was used as the donor and another as the skin graft recipient. In two instances reciprocal grafts were made between two chicks (fig. 1, nos. 319 and 320). All grafts were 1 cm.^{2} in size. Spleens pooled from 7 WL chickens were decapsulated, minced with scissors, suspended in Hank's solution and injected subcutaneously into 3 NH chickens. One of the injected chickens became weak and thin 7 days after injection and was killed.

The homografted chickens were bled from the heart at 4- to 7-day intervals. Sera thus collected were stored at −10°C., and heated to 56°C. for 30 minutes before use in accordance with the procedures used in leukoagglutination tests.[5, 11] Lymphocytes for the test were isolated from the blood of the skin graft donor chicken by techniques described previously.[18] For tests of the sera of chickens injected with pooled spleens, lymphocytes were taken from normal WL chickens (other than spleen donors). Lymphocytes were added to doubling dilutions of sera from the grafted or injected animals in agglutination wells, and incubated for 2 hours at 37°C. as in previous tests.[19]

RESULTS

Skin homografts on all 3 adult chickens were sloughed within a period of 2 weeks. Shortly thereafter a very sharp rise in the lymphoagglutinin titer was obtained in the sera of two chickens (fig. 1). The peak titer was reached in the serum of both birds at 3 weeks after grafting, and declined to zero at 5 and 6 weeks after grafting. No lymphoagglutinins, however, were demonstrable in one grafted bird up to 5 weeks after grafting.

Four-day-old chicks which sloughed their homografts within 2 weeks after grafting showed some development of lymphoagglutinins (fig. 1). However, only one-half of the birds developed significant titers, and the peak titers were reached considerably later than in adult birds. Lymphoagglutinating activity of the sera persisted up to 10 weeks after grafting in two instances. Sera from

* From the Department of Surgery, University of California Medical Center, Los Angeles 24, California.

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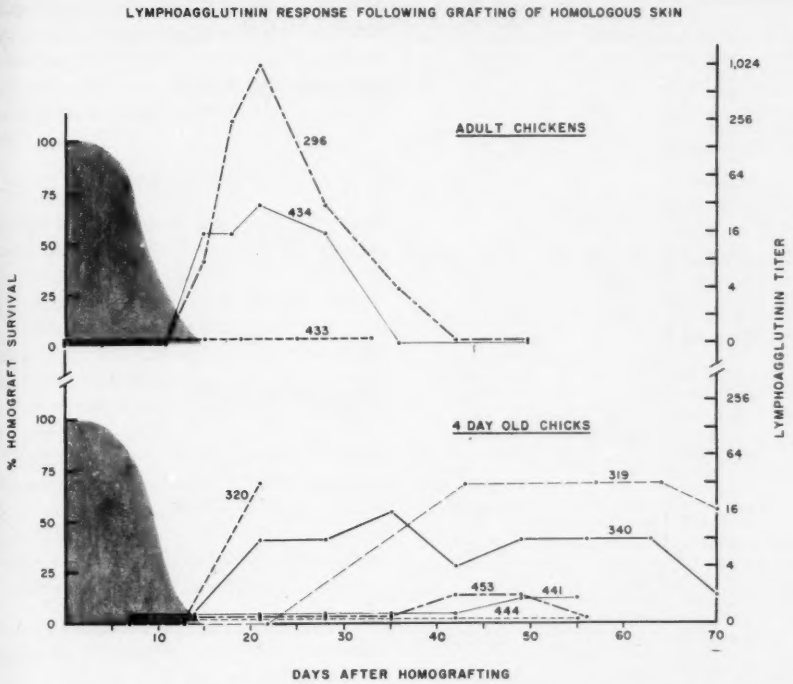

FIG. 1. Adult chickens and 4-day-old chicks were homografted with adult and 4-day-old chick skin respectively. The per cent of homograft survival is indicated by *shaded area*. The sera of the grafted birds were tested with the lymphocytes of the skin donor and the titer of the sera of each grafted bird is shown by the *lines*.

chickens injected with pooled spleens and tested with lymphocytes from chickens other than the spleen donors yielded somewhat similar results to that following homografting of skin. As might be expected, since the animals were injected with spleens from many chickens, various different responses were found when their sera are tested with lymphocytes of other chickens (fig. 2). Lymphoagglutination was not found in any instance on the 4th day after injection of pooled splenic cells, but was present in most instances by the 8th day. A rise in the titer and gradual decline occurred with the serum of chicken no. 309, but was quite irregular with the serum of chicken no. 5 (fig. 2). The possibility that this irregularity is attributable to technical difficulties is now being investigated. The persistence of antibodies in the serum was substantially longer following injection of spleens than after transplantation of skin in adults (*cf.* figs. 1 and 2).

DISCUSSION

The occurrence of a humoral antibody response to homografts has been reviewed by Gorer,[7] Snell,[16] and others. As has been pointed out by Walford,[20] the appearance of leukoagglutinins after transfusion in humans is an instance of humoral response to homografts. These leukoagglutinins have been conclusively shown to appear upon transfusion of blood in humans by statistical analysis (Payne[15]), and by observations of the development of agglutinins during repeated transfusion (Dausset[6]). In a normal human subject, leukoagglutinins have been shown to appear upon intravenous injection of 100 ml. of blood at weekly intervals for 9 weeks.[3] That leukoagglutinins may exert some effect on leukocytes *in vivo* is supported by the occurrence of leukopenia in many individuals possessing leukoagglutinins (Killmann[10]).

Thus, it seems likely that injection of homol-

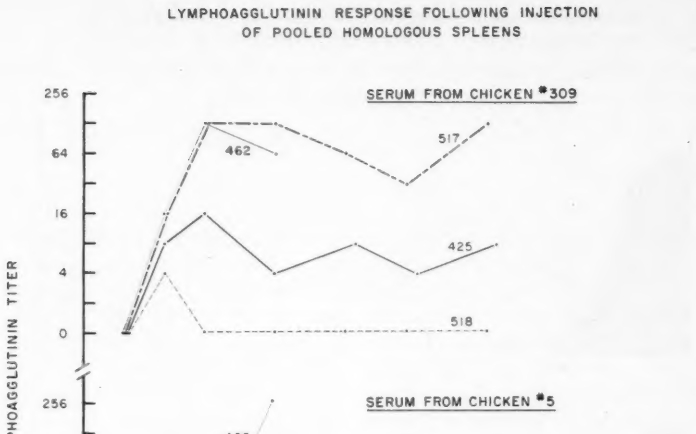

FIG. 2. Two adult chickens were injected with pooled homologous spleens from 7 chickens. The sera from these injected birds were tested with lymphocytes from chickens other than the spleen donors. Lymphoagglutination titers are plotted against time.

ogous leukocytes elicits a humoral antibody response directed against leukocytes. That skin grafts can also elicit such a response has been demonstrated by Amos and associates.[2] We have reported similar results using a lymphoagglutination technique.[19] In the present work, the time of appearance of the lymphoagglutinating power of sera from homografted animals seems to agree quite well with what might be expected if lymphoagglutination were caused by antibodies. Thus, although no lymphoagglutinins were found 4 to 7 days after either the grafting of skin or injection of splenic cells, lymphoagglutinins appeared in the serum at about 2 weeks and reached a maximum about 3 weeks after grafting or injection.

Detection of lymphoagglutinins in the blood shortly after the completion of sloughing of the skin suggests that these agglutinins may play some role in the destruction of grafts. That is, these antibodies may be absorbed by the skin graft as they act upon the graft, and may be spilled over into the circulation only after the graft has been destroyed. On the other hand, our present data can also be interpreted to show that lymphoagglutinins do *not* play a role in the rejection of homografts. First, although the 6 selected 4-day-old chicks sloughed their homografts as rapidly as the adult chickens tested, lymphoagglutinin titers were higher and appeared earlier in the sera of the adults. However, it is quite possible that visual assessment of skin graft survival was not accurate and that the agglutination reaction was a more delicate index of the response to homologous antigens. Secondly, about one-half of the animals which rejected homografts rapidly could not be shown to develop lymphoagglutinins in significant titers. Thus far, we have no good explanation for this finding. Attempts are being made to determine whether these instances in which an animal sloughs homografts but apparently does not form lymphoagglutinins

can be ascribed to technical difficulties. Although lymphocytes share more antigens in common with skin than the red blood cells do,[12] it is possible that lymphoagglutinins, like hemagglutinins,[9, 14] do not necessarily play a role in the homograft reaction.

SUMMARY

Following homografts of skin in adult chickens and 4-day-old chicks, the sera of the grafted animals were shown to acquire the ability to agglutinate blood lymphocytes of the skin donors. This lymphoagglutinating activity of serum from homografted animals first appeared 2 weeks after grafting and reached a maximum at about 3 weeks. Chickens injected with pooled homologous splenic tissue also produced lymphoagglutinins in 2 to 3 weeks. The time of appearance of the lymphoagglutinating activity of the serum is consistent with the idea that it is caused by an antibody. Whether these antibodies may also be responsible for the destruction of homografts such as skin cannot yet be answered.

University of California Medical Center
Los Angeles 24, California

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TRAUMATIC RUPTURE OF THE SPLEEN*

BERYL D. AVERBOOK, M.D., AND SEIBERT PEARSON, M.D.

Los Angeles, California

Splenic rupture is frequently seen in an institution dealing with the acutely injured. Los Angeles County is a widespread metropolitan area with the highest concentration of automobiles in the country. With crowded highways and freeways it is logical that the automobile is responsible for the majority of the increasing number of traumatic abdominal injuries. Many of these patients have multiple injuries and it is inevitable that some will expire before they can receive surgical treatment.

There have been 73 patients with traumatic splenic rupture admitted to Harbor General Hospital from 1946 through May 1959. There were 3 patients with penetrating wounds; the others sustained blunt trauma. The ages ranged from 18 months to 65 years. There were 18 cases under the age of 14, 7 between 14 and 20, 28 between 20 and 40, and 11 between 40 and 70. There were 4 operative and 3 nonoperative deaths, a mortality which compares favorably with other reports.

Parsons and Thompson[4] report a 12 per cent mortality in 26 cases of nonpenetrating trauma and no operative deaths. Terry and associates[6] report a mortality of approximately 25 per cent in a series of 102 cases, 49 of which had penetrating, and 53 blunt injuries. Byrne[1] reported a series of 101 cases from the Los Angeles County Hospital with an operative mortality of 16.8 per cent.

In our present study we became particularly interested in patients who died without benefit of surgery, and in whom diagnosis was confirmed by autopsy. Cloutier and Zaepfel[2] reported a series of 43 cases; 10 of these patients were considered poor surgical risks because of multiple injuries, persistent shock, or both, and were not operated. All 10 patients died, and in none was a diagnosis of ruptured spleen suspected before death, although 2 lived 9 days.

* From the Department of Surgery, University of California Medical Center, Los Angeles, California, and the Department of Surgery, Los Angeles County Harbor General Hospital, Torrance, California.

We realize that a difficult problem exists when other severe injuries are present, and that abdominal exploration in these patients is associated with a high mortality. There were 34 patients with multiple injuries who had emergency splenectomy and the operative mortality was 11.8 per cent. Traumatic chest, extremity fractures, pelvic fractures, lacerated liver and fractured or contused left kidney were the most frequently encountered associated injuries. To emphasize some of the problems in the management of these severely injured patients, 3 cases of nonoperative deaths are summarized below.

CASE REPORTS

Case 1. C. M., a 60-year-old white man, was admitted to the orthopedic service December 17, 1956, 11 hours after an automobile accident. His blood pressure was 160/85; the pulse, 80 per minute; hemoglobin 13.6 gm.; and the white count 14,400 cells per cc. There was a fracture of the 5th cervical vertebra with posterior displacement of the 6th cervical vertebra. The abdomen was soft, with active peristalsis. Crutchfield tongs were applied and excellent alignment resulted. There were no neurologic findings. He expired 6 days later probably because of an acute myocardial infarction. A coroner's autopsy showed a ruptured spleen and a terminal bronchopneumonia.

Case 2. G. B., a 30-year-old white man, was admitted on September 21, 1956, 30 minutes after a motorcycle accident. He was unconscious; the blood pressure was 175/90; the pulse 150 per minute; hemoglobin 11.9 gm.; hematocrit 40 per cent; and temperature 102 rectally. There were multiple injuries of the head, decerebrate rigidity, and hematuria. A peritoneal tap was negative. A tracheotomy was done on September 22, and on September 23 a left temporoparietal burr hole was made and an edematous cerebral cortex was found. The pupils became dilated, irreversible shock developed, and he expired on September 25, 1956. A coroner's autopsy showed terminal bronchopneumonia with rupture of the spleen and left kidney.

Case 3. C. S., a 17-year-old Negro woman, was admitted on July 10, 1957, 2 hours after an automobile collision. Her blood pressure was 96/0; the pulse 110 per minute; hemoglobin 8.6 gm.; and hematocrit 33 per cent. There was marked ab-

dominal rigidity and a peritoneal tap was positive for blood. There were multiple contusions of the face, a fractured right humerus, and a questionable lung laceration. She was given 1500 cc. of Dextran. A tracheotomy was performed because of respiratory difficulty, and she was taken to surgery 1 hour after admission. Blood was started and 15 minutes later, with a blood pressure of 110/70, a spinal anesthetic (10 mg. of Pontocaine) was given. Her blood pressure became imperceptible and respirations ceased 12 minutes after administration of the anesthetic. Autopsy showed laceration of the mediastinum and spleen with thoracic and abdominal hemorrhage.

The deaths in these 3 cases were probably unavoidable; however, in case 3 there may have been a better chance for survival if more thought had been given to the choice of anesthetic and to adequate preoperative blood replacement. A sudden fall in blood pressure occurs frequently with spinal anesthesia and in the actively bleeding patient will increase the incidence of cardiac arrest. Lorhan[3] recommends cyclopropane with endotracheal intubation as the anesthetic of choice. Dextran gave the surgeon a false sense of security and insufficient blood was given. Hypoxemia was certainly increased by the mediastinal and thoracic hemorrhage and contributed to cardiac and respiratory arrest.

A peritoneal tap would have been beneficial in establishing an early diagnosis in cases 1 and 2, and abdominal exploration may have been possible in case 1. We feel that patients with extensive multiple injuries including cerebral contusion and cervical fracture must be operated if intraperitoneal bleeding is evident.

The 4 cases of operative mortality are summarized:

Case 1. E. B., a 24-year-old white woman, was admitted on June 12, 1956, 52 minutes after an auto accident. Her blood pressure was 74/0; the pulse 150; hemoglobin 11.3 gm.; and white blood count 11,200 cells per cc. A peritoneal tap was positive for blood. There were fractures of the left 7th and 8th ribs. She received 4000 cc. of blood before surgery, but without effect. She was taken to surgery 5½ hours after admission, but before any anesthetic was given cardiac arrest occurred. Cardiac massage was begun within 4 minutes after the arrest and the abdomen was explored approximately 20 minutes later. Operative findings consisted of multiple lacerations of the spleen, a large volume of intraperitoneal blood, and a massive retroperitoneal hematoma. The patient expired before the operation was completed. During surgery 4500 cc. of blood were given.

Case 2. D. K., a 34-year-old white woman, was admitted on January 16, 1958, 4 hours after an automobile accident. Her blood pressure was 170/70; the pulse 80 per minute; hemoglobin 13.4 gm.; hematocrit 39 per cent; and white blood count 52,400 cells per cc. There were fractures of the left 5th to 9th ribs, a fracture of the transverse process of L-1, and an elevated left diaphragm. There were moderate abdominal rigidity and hypoactive bowel sounds. A peritoneal tap was positive for blood. Dextran, 500 cc., and blood, 500 cc., were given, and surgery was performed 30 minutes after admission. There was a lacerated spleen with 1500 cc. of intraperitoneal blood. During surgery 500 cc. of blood were given. She did well until the 6th postoperative day, when she developed abdominal distention, hypotension, tachycardia and anuria. Roentgenograms showed dilated small and large bowel with some air fluid levels. She was re-explored because of persistent hypotension, fever of 105 and resistance to all therapy. Bilateral subphrenic abscesses and a right subhepatic abscess were drained. She expired shortly after surgery because of overwhelming septicemia.

Case 3. B. L. S., a 29-year-old white man, was admitted January 10, 1953, after a motorcycle accident. The blood pressure was 110/48; the pulse 80 per minute; hemoglobin 10.5 gm.; and white blood count 44,600 cc. There was generalized abdominal tenderness with moderate rigidity and absent bowel sounds. There was a 3-cm. puncture wound of the left upper abdomen. Two units of plasma and 1000 cc. of blood were given and he was explored 3 hours after admission. At surgery there was avulsion of the entire small bowel mesentery with an estimated 1000 cc. of fresh blood in the peritoneal cavity. There was a laceration of the spleen and a small perforation of the stomach. He was given 7500 cc. of blood, but expired on the operating table.

Case 4. R. B., a 29-year-old white man, was admitted on December 5, 1951, approximately 1½ hours after being crushed between a bus and a pillar. The blood pressure was 80/60; the pulse 100 per minute; and hemoglobin 12.5 gm. There were marked abdominal rigidity, a left hemothorax and a fractured right scapula. A peritoneal tap was positive for blood. He was taken to surgery 6 hours later, having received 1 unit of plasma and 1500 cc. of blood. There was a large laceration of the liver, a deep laceration of the spleen, and a left retroperitoneal hematoma. During surgery 1500 cc. of blood were given. An additional 1000 cc. of blood were given in the early postoperative

period, elevating the hemoglobin to 15 gm. The patient suddenly went into shock on the 3rd postoperative day, with dilated neck veins, cyanosis and a dusky appearance about the head and nipples. The impression was superior mediastinal hemorrhage, with superior vena caval obstruction. Cardiac arrest occurred during bronchoscopy, but the heart beat returned spontaneously. The patient died 3 hours later. A coroner's autopsy showed anterior mediastinal contusion and hemorrhage. There was partial collapse of both lower lobes and the bronchi contained large mucous plugs.

Multiple injuries were present in all 4 cases. The death of case 2 was the result of toxemia from subhepatic and subphrenic abscesses. Case 1 demonstrates the futility of multiple transfusions when bleeding is rapid and continuous. Surgical intervention is urgent in such situations and must be undertaken even in the presence of hypotension. The death of case 3 was due to a severe crushing injury of the chest, and case 4 acquired irreparable damage to the small bowel mesentery.

DISCUSSION

Diagnosis. A positive peritoneal tap in the face of trauma is definite indication for abdominal exploration; 32 patients had a peritoneal tap and this was positive in 29 cases. All four abdominal quadrants should be aspirated before considering a tap negative, since blood may be confined to one area. If the initial tap is negative, careful observation and evaluation of physical findings are necessary and repeat taps should be done at frequent intervals. There were 3 patients in whom a peritoneal tap was positive several hours after a negative examination.

Early abdominal palpation may reveal a soft abdomen, but there is usually a progressive increase in abdominal rigidity and tenderness with a drop in hemoglobin and hematocrit. Roentgenograms in some cases will show an elevated diaphragm, a suspicious left upper quadrant mass, and the gastric air deviated to the right. Delayed rupture is not infrequent, and an inadequate history makes the diagnosis more difficult. There were 4 cases of delayed rupture in which acute symptoms did not occur until at least 48 hours after injury.

An interesting case of hemorrhage in the spleen without rupture into the peritoneal cavity is that of a 34-year-old white woman who fell against the handlebars of a bicycle and injured her left rib cage. Approximately 7 days later she had sudden onset of dyspnea and was hospitalized in New York City with a collapsed lung. She was told that she had a blood clot in the spleen and was treated conservatively. She was seen at Harbor Hospital 6½ months later with an enlarged spleen and in view of the past history splenectomy was performed. Surgery disclosed a large subscapular hematoma without rupture.

Patients with slight trauma and minimal blood loss present a more difficult diagnostic problem and we have found this more frequent in children. Pender[5] emphasizes that localized tenderness over the spleen and Kehr's sign are the most important early physical signs.

In our series of 18 pediatric patients we have found peritoneal tap to be the most reliable procedure and it was positive in 8 patients in which this was attempted. In 1 child the initial tap was negative, but 3 hours later a repeat tap was positive. With a positive abdominal tap the average time interval between admission and surgery was 5 hours; without abdominal taps the average time interval was 11 hours. The value of the four quadrant peritoneal tap in children, therefore, cannot be overemphasized.

Treatment. Whole blood should be started in all cases of ruptured spleen as soon as it is available and we recommend cannulating one or two extremity veins for its administration. If necessary, plasma or plasma expanders may precede the blood.

With massive intraperitoneal hemorrhage the possibility of blood loss from the inferior vena caval or portal vein systems exists. Such a situation was encountered in a 2-year-old girl with multiple tears in the inferior vena cava. A large volume of blood was given rapidly in a lower extremity vein, but most of the blood accumulated in the peritoneal cavity and she expired before the bleeding could be controlled. She would have had a better chance for survival if blood had been given into a cannulated upper extremity vein.

If a patient fails to respond after 2 to 3 units of blood, bleeding must be massive and continuous and surgery is urgent. Blood should then be given rapidly until the peritoneal cavity is opened and bleeding controlled. Patients who do not receive adequate blood replacement before operation are more susceptible to shock during

surgery. The amount of blood to be given before surgery is best determined by clinical and, secondarily, by laboratory findings. Overtransfusion in children should be avoided; nevertheless, we prefer to start blood in all children with a ruptured spleen before surgery. A child with minimal blood loss and a hemoglobin value of 11 or 12 gm. is no exception. The average volume of blood given to 12 children under 14 years of age without evidence of shock was approximately 700 cc. The average volume of blood given to 5 children with shock was 1375 cc.

The principal reason for starting blood before surgery is that a certain amount of intraperitoneal tamponade exists, and upon opening the abdomen and manipulating the abdominal viscera, we have observed marked acceleration of bleeding. The peritoneal cavity may be entered through a left paramedian or subcostal incision. The spleen should be removed as quickly as possible and the pedicle controlled digitally until the vessels can be clamped. Drainage of the left subphrenic space is advised to remove excess blood and possible pancreatic secretion if the tail of the pancreas has been injured.

One should be aware of the increased tendency for thrombosis with postsplenectomy platelet elevations. Adequate hydration may help prevent thrombophlebitis and pulmonary infarction, and we have given anticoagulants to 2 patients with platelet counts of 1,000,000 or over.

Complications. After splenectomy a large subphrenic space remains which may accumulate blood and pancreatic secretion. This may result in a subphrenic abscess, and has occurred 4 times in our series. Subphrenic abscesses are more frequent in patients with delayed splenic rupture due to chronic inflammation involving the diaphragm and spleen.

We have had 2 cases of bleeding from short gastric arteries which necessitated re-exploration. At the initial surgery extreme care should be taken to ligate all the greater curvature vessels, since thrombosed vessels may bleed later.

An unusual complication in 1 patient was a benign stricture of the splenic flexure which was repaired 9 months after splenectomy. An ileocolic intussusception was the cause of post-operative small bowel obstruction in a 9½-year-old boy with a ruptured spleen and kidney.

Wound dehiscense has occurred 3 times and impaired tissue healing may have some relationship to splenectomy. Wilson[7] reports 3 cases of splenectomy with delayed tissue repair. Other complications have been atelectasis, pneumonitis, pleural effusion, pulmonary infarction, and wound infection.

SUMMARY

1. Seventy-three cases of traumatic rupture of the spleen have been reviewed with an over-all mortality of 9.7 per cent, and operative mortality of 5.4 per cent.

2. In cases of abdominal trauma a positive peritoneal tap is indication for surgery.

3. One negative tap does not rule out splenic rupture and repeated taps may be positive. Careful observation is required when abdominal taps are negative.

4. Multiple injuries decrease the patient's chances for survival.

5. Abdominal exploration should not be withheld in cases of intraperitoneal bleeding associated with multiple injuries.

6. The intelligent use of whole blood in adequate amounts is recommended.

7. Proper choice of anesthesia is necessary. Cyclopropane has been recommended as the agent of choice.

8. Complications following splenectomy are mentioned.

Dr. Beryl D. Averbook
University of California Medical Center
Los Angeles 24, California

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SURGICAL CORRECTION OF ANOMALOUS PULMONARY VENOUS DRAINAGE WITHOUT ATRIAL SEPTAL DEFECT: A CASE REPORT*

PETER G. GAAL, M.D., AND JAMES V. MALONEY, JR., M.D.

Los Angeles, California

The anomalous drainage of one or more pulmonary veins into the right side of the heart produces an undesirable physiologic burden. Although anomalous pulmonary venous drainage was once an anatomical curiosity, it has now assumed importance because it is frequently encountered during operations for the correction of cardiac defects. Most cases are associated with an atrial septal defect, and it is during operations for this latter condition that the surgeon often finds abnormal pulmonary veins. The high incidence of atrial septal defect in association with anomalous pulmonary venous drainage is fortunate, for the additional defect often facilitates surgical repair. The purpose of this communication is to describe a new operative procedure applicable in those rare instances when there is no atrial septal defect in association with anomalous pulmonary venous drainage into the superior vena cava.

CASE REPORT

J. R. M. (UCH,LA, 015-30-39), an 8-year-old white boy, was first noted to have a heart murmur at 18 months of age. Cardiac catheterization was performed at age 2 and repeated 6 months later; however, no definitive diagnosis was made following these studies. At the time of his initial visit to the University of California Medical Center, Los Angeles, his parents stated that the child's growth and development during infancy had been normal. He had never been cyanotic and apart from a bout of cystitis at the age of 5 had been in good health throughout life. During the 6 months before his visit, he complained of increasing fatigability and was noted to be somewhat less active than formerly. The family history was unremarkable.

Physical examination revealed a small, slender, active child in no apparent distress. The pulse rate was 88, respiratory rate 22, and blood pressure 80/45. Cardiac rhythm was normal. A grade III systolic murmur was heard along the high left sternal border and in the interscapular area. A grade II, mid-diastolic murmur was present along the lower left sternal border and was transmitted to the apex. A mild precordial heave was present. The remainder of the examination was unremarkable.

Routine chest films revealed slight cardiomegaly with some increase in pulmonary markings. The cardiac silhouette suggested right ventricular enlargement. Electrocardiographic studies were interpreted as showing combined ventricular hypertrophy with normal electrical axis. Repeat cardiac catheterization showed an anomalous pulmonary venous connection between the right upper lung field and superior vena cava. The presence of an interatrial septal defect was suspected but not confirmed.

The patient underwent surgery on March 5, 1959. The chest was opened through a bilateral thoracotomy in the fourth interspace. Venous drainage of the right upper and middle lobes formed a common trunk which entered the superior vena cava 2.3 cm. above the right atrium (fig. 1*A*). The inferior division vein on the right side drained normally into the left atrium. All other great vessels and the general appearance of the heart were normal.

A finger was inserted into the right atrium through a purse-string suture in the atrial appendage. No atrial septal defect was palpated. At this point in the procedure, pulmonary resection was considered but rejected because of the necessity of removing both the right upper and middle lobes. The pericardium was then dissected from around the pulmonary veins and left atrium in an effort to determine if a direct anastomosis between the anomalous venous trunk and left atrial wall was feasible. The distance between superior vena cava and left atrium precluded this possibility. The right common femoral artery was then cannulated, catheters were placed through the right atrial appendage into the superior and inferior venae cavae, and extracorporeal circulation was initiated.

The right atrium and the lower 3.0 cm. of the superior vena cava were opened, using a longitudinal incision (fig. 1*B*). Bronchial venous drainage through the anomalous pulmonary vein was

* From the Department of Surgery, University of California Medical Center, Los Angeles, California.

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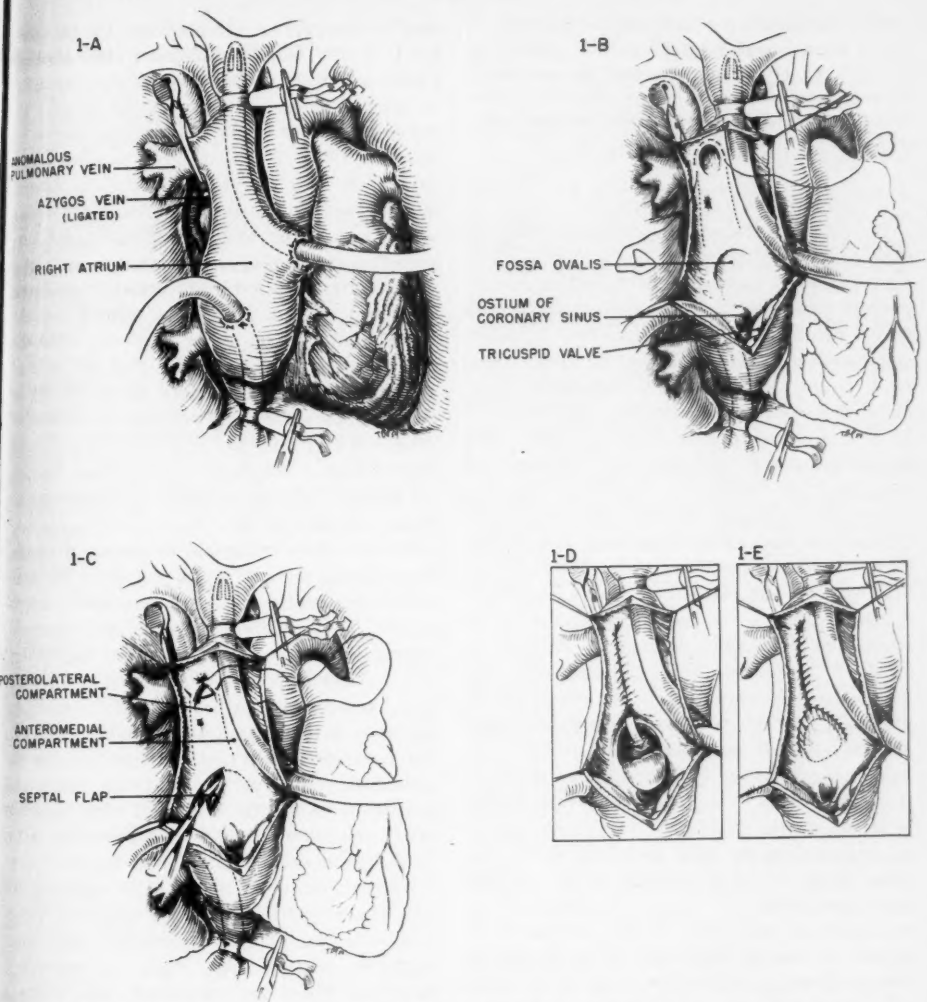

FIG. 1, *A* to *E*. Correction of isolated anomalous pulmonary drainage into superior vena cava. See text for description of surgical procedure.

controlled by intermittently occluding the vessel. A continuous suture was placed inside the superior vena cava and continued downward toward the right atrium so that the vessel was divided into 2 separate compartments (fig. 1*C*). The anteromedial compartment contained the venous cannula draining blood from the upper half of the body; the posterolateral compartment carried blood from the anomalous pulmonary vein. The azygos vein was ligated to prevent mixing of systemic and pulmonary venous blood in the latter channel. A semicircular incision, convexity cephalad, was made in the interatrial septum creating a large defect (fig. 1*D*). The flap thus created was then sutured to the right atrial wall so as to divert pulmonary venous blood draining down the posterolateral compartment of the superior vena cava through the newly created atrial septal defect into the left atrium (fig. 1*E*). Systemic venous return from the upper half of the body drained through the anteromedial compartment into the right atrium as before. Extracorporeal circulation was discontinued and the venous drainage catheters immediately removed.

The postoperative course was noteworthy in that a third degree heart block was present for the first 10 days. This resolved spontaneously without residual cardiac irregularity. The child is now completely asymptomatic 2 months after surgery.

DISCUSSION

The diagnosis of anomalous pulmonary venous drainage, once considered a rare entity, is made more frequently as progress in evaluating cardiac patients continues. Since Brody's classic report of 106 cases,[4] Dotter and associates,[5] Friedlich and associates,[7] Healey,[9] Edwards,[6] Gould,[8] and most recently Bahnson and associates,[2] have reported series of patients with this anomaly. It is interesting to note that over 200 years transpired between the time the condition was recognized by Winslow in 1739 and diagnosed during life by Taussig in 1947.[15] Brantigan[3] and Dotter and associates,[5] recognizing the cardiac burden produced by this abnormality, suggested lobectomy or pneumonectomy for its correction. A major advance in the surgical treatment of anomalous pulmonary drainage is credited to Muller,[12] who successfully anastomosed an anomalous pulmonary vein to the left atrium in correcting partial anomalous venous drainage. Recent technical accomplishments greatly facilitate surgical correction of anomalous drainage. The first of these is shifting of the atrial septum when anomalous pulmonary venous drainage is associated with an atrial septal defect.[2, 11] Another is the compartmentation of the superior vena cava into two channels as described by Bahnson and associates.[2] Neither of these techniques is directly applicable when pulmonary venous drainage into the superior cava occurs without an accompanying atrial septal defect.

The life expectancy of patients with anomalous pulmonary venous drainage is unfortunately unknown, although it is evident that total anomalous drainage carries a far less favorable prognosis than partial abnormal return. Brody,[4] and later Hughes and Rumore,[10] believed that important clinical signs are to be expected only if more than 50 per cent of the pulmonary venous blood is abnormally shunted to the right side of the circulation. Snellen and Albers[14] and Smith[13] concluded that most patients with partial abnormal pulmonary venous drainage maintained good health until an advanced age. On the other hand, Healey found that among 147 cases of partial and total anomalous drainage examined at autopsy the average age was 5.8 months. Of the 44 cases of incomplete drainage collected by Brody in 1942, 35 patients lived to adult life; 9 died before their 1st year. The work of Adams[1] and others, based in part upon autopsy studies of newborn infants and premature infants, suggests that the over-all picture is not as optimistic as formerly supposed regarding the prognosis in untreated cases. These data suggest that the mortality from this disease is greater than the risk of surgery. It is probable that all patients with a significant left-to-right shunt should be operated upon. The incidence of major complications, chiefly pulmonary hypertension and right heart failure, is significant to the extent that we are inclined to treat routinely even the asymptomatic young patient.

In most cases of anomalous venous drainage, the surgeon's primary attack will be on the associated atrial septal defect which is almost always present. The correction of anomalous pulmonary venous drainage will be of secondary importance and frequently may be accomplished at the same time. An operative procedure of the complexity described in this presentation is rarely indicated. Our preference in the past has been to divide the anomalous vein from the systemic vessel and anastomose it directly to the left atrial wall, left atrial appendage, or an adjacent pulmonary vein. If the anomalous drainage had involved only the upper lobe or one or two of its segments, we would have elected to perform a pulmonary resection, since resection would certainly carry lower morbidity and mortality than the procedure described. When the anomalous vein drains a significant portion of the total pulmonary bed, surgery of the type described probably offers a better long term result than pulmonary resection.

SUMMARY

This communication describes an operative procedure for those rare instances in which there is no atrial septal defect in association with an anomalous pulmonary vein draining into the superior vena cava. By the open heart technique, partitioning of the superior cava and creation of an interatrial defect, redirection of pulmonary

venous return to the left atrium is accomplished. A case presentation is included.

Dr. Peter G. Gaal
University of California Medical Center
Los Angeles 24, California

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RECURRENT COARCTATION OF THE AORTA IN INFANCY*

DONALD G. MULDER, M.D., AND LEONARD M. LINDE, M.D.

Los Angeles, California

The surgical treatment of coarctation of the aorta in children and adults by excision of the stenotic segment and end-to-end anastomosis is well established.[6] A high mortality rate in certain infants with this disease,[2, 4] despite intensive medical management, has stimulated earlier surgical intervention.[1, 3, 7]

In view of this, it seemed pertinent to report a complication of such surgery which is probably unique in this age group; namely, a recurrence of a successfully resected coarctation of the aorta in a 2-week-old infant.

CASE REPORT

C. O'C. (UCH, LA, 015-23-68), a white female, was first admitted to the University of California Medical Center, Los Angeles at the age of 10 days. At birth, tachypnea with cyanosis of the hands, feet and lips was noted. At the age of 9 days, she required digitalization for congestive heart failure.

Physical examination revealed an acutely ill, tachypneic infant with an enlarged heart, faint femoral arterial pulsations, and marked hepatomegaly. Blood pressure (flush technique) was 60 mm. Hg in the arms and 30 mm. Hg in the legs. The electrocardiogram was consistent with marked right ventricular hypertrophy.

Treatment consisted of digitalis, mercurial diuretics, low salt diet, and oxygen. The patient failed to respond to 3 days of medical management and because her condition remained critical she was taken to surgery with the preoperative diagnosis of coarctation of the aorta. At operation a severe coarctation was found with a patent ductus arteriosus inserting into the distal aorta. Just proximal to the coarctation a right subclavian artery arose anomalously and passed behind the esophagus to the right side (fig. 1). Occluding clamps were placed above and below the coarctation and on the pulmonary end of the ductus arteriosus. The stenotic segment was removed and the proximal and distal aortic ends trimmed back to a normal sized lumen. The ductus was then closed, following which a satisfactory end-to-end aortic anastomosis was performed. Upon release of the occluding clamps, a good pulsation was present in the distal aorta. The patient tolerated the procedure well. The immediate postoperative course was characterized by marked improvement. Femoral pulsations were normal and within 24 hours the previously enlarged liver was no longer palpable.

The patient was discharged 2 weeks after operation, at which time her respirations varied between 60 and 80 per minute. Femoral pulsations were easily palpable and of good quality, but flush blood pressures were recorded at 60 to 70 mm. of Hg in the arms and 40 to 42 mm. of Hg in the legs. The liver was 1 cm. below the right costal margin. Radiographic examination of the chest revealed persistent cardiomegaly, but some decrease in the previous excessive pulmonary vascularity.

The patient was readmitted 5 weeks after surgery because of cyanosis, vomiting, weakness, fatigue and tachypnea. Femoral pulsations were now absent and flush blood pressures were 110 mm. of Hg in the arms and 60 mm. of Hg in the legs. The electrocardiogram and chest roentgenogram remained unchanged from the previous examination.

Cardiac catheterization was performed 6 weeks postoperatively (table 1). The femoral artery was isolated and a catheter passed retrograde into the proximal aorta and right carotid artery where the systolic pressure was 132 mm. of Hg. The systolic pressure fell sharply to 60 mm. of Hg as the catheter was withdrawn across the anastomotic site into the distal aorta (fig. 2). Injection of radiopaque material into the proximal aorta revealed definite narrowing in the region of the previous repair (fig. 3). The catheter was withdrawn, placed in the saphenous vein, and passed up into the right ventricle where the pressure was 100/0 mm. of Hg. An angiocardiogram with selective injection into this chamber demonstrated an enlarged right ventricle and a very small left ventricle.

Re-exploration was performed 7 weeks after the initial operation. Grossly, the anastomotic site appeared normal; however, no pulsation was present in the distal aorta. Proximal and distal aortic

* From the Department of Surgery and Pediatrics, University of California Medical Center, Los Angeles 24, California.

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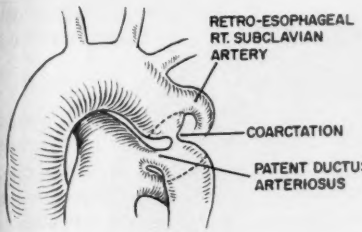

FIG. 1. Diagram illustrating findings at surgery in the case reported. A patent ductus arteriosus communicated with the distal aorta. A very large retroesophageal subclavian artery arose just proximal to the coarctation.

TABLE 1

*Cardiac catheterization data of patient C. O'C. performed between first and second coarctation repair**

Site	Pressure	Oxygen Saturation
	mm. Hg	%
Right ventricle (mid)	108/0	74
Right ventricle (apex)	100/0	74
Right atrium (high)	10/6	71
Right atrium (low)	10/7	71
Left atrium	15/8	89
Right carotid artery (proximal to coarctation)	132/54	89
Abdominal aorta (distal to coarctation)	60/42	89

* Impression: Marked pulmonary hypertension, coarctation of aorta.

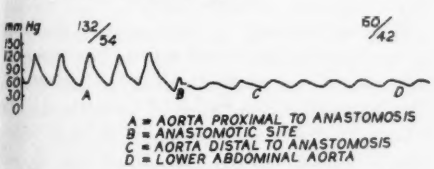

FIG. 2. Pressure tracing obtained by withdrawing catheter across the site of first coarctation repair demonstrating a systolic gradient of 72 mm. of Hg.

clamps were applied and the stenotic segment removed. An end-to-end anastomosis was successfully performed, although frequent pauses were necessary to allow improvement of the faltering heart action. The occluding clamps were cautiously released during which time the heart action deteriorated. Despite reapplication of the clamps, cardiac massage and intracradiac medications, the heart could not be resuscitated. Gross and histologic examination of the resected specimen (fig. 4) revealed marked proliferative changes in the aortic wall identical to those in the initial specimen. Only a 1-mm. lumen remained. There was no evidence of thrombus formation. A hypoplastic left ventricle was the only other cardiac abnormality.

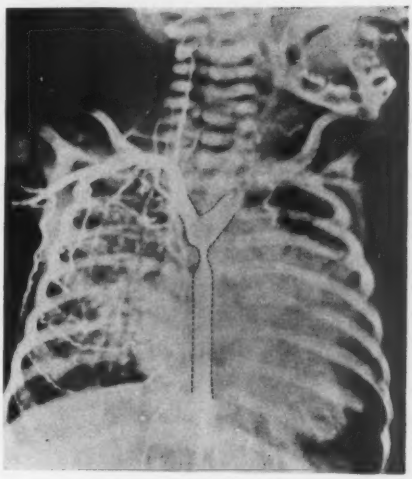

FIG. 3. Angiogram obtained by injection of radiopaque material into thoracic aorta proximal to anastomosis. Coarctation has reformed at site of previous repair. Extensive collateral circulation can be seen.

DISCUSSION

It has been suggested that the optimal age for surgical treatment of coarctation of the aorta is 8 to 12 years.[6] However, the high incidence of death from coarctation in infancy has been known for many years[2, 4] and has been excellently reviewed by Mustard and associates.[7] In their series, an 89 per cent mortality was noted in infants with preductal coarctation, whereas the mortality in the postductal variety was 60 per cent. Although surgery should be delayed in the minimally symptomatic infant, the severely ill patient with uncontrollable heart failure is an urgent surgical candidate. Reports indicate that coarctation repair is feasible in the 1st year of life, even in infants as young as 2 weeks of age.[1, 3, 6, 7]

Operations in this age group pose certain technical problems. Delicate dissection and a meticulous anastomosis are essential in dealing with these small vessels. Despite such precautions in

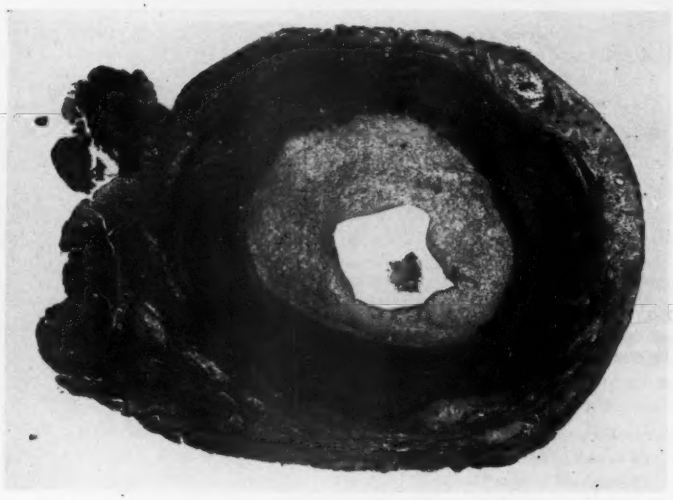

FIG. 4. Photomicrograph of recurrent coarctation resected at second operation

the case reported, a recurrent coarctation formed at the site of the previous repair. The presence of a patent ductus arteriosus communicating with the distal aorta, and a very large retroesophageal right subclavian artery arising immediately proximal to the coarctation, made resection of this area somewhat more difficult. The anomalous subclavian artery was not completely occluded because its large size suggested that it might be supplying a significant part of the cerebral blood flow. The aorta was transected through the coarcted segment in an effort to save as much proximal aortic tissue as possible, and each end then trimmed back to a normal sized lumen. The anastomosis was completed without undue difficulty and a strong pulsation was immediately present in the distal aorta. The dramatic clinical improvement with strong femoral pulsations suggests that the subsequent recurrence of the coarctation was not due to an initial failure to restore a normal sized lumen, but rather an actual redevelopment of the obstructive process. Gross and microscopic examination of the specimen resected at the second operation indicates this to be the probable sequence of events.

D'Abreu and Parsons[5] have reported a similar occurrence in a 9-month-old female. Reformation of the coarctation at the site of the anastomosis over a period of a "few weeks" was demonstrated on angiography. No reoperation was performed. The success of the initial coarctation repair in our case was amply demonstrated by the fall in blood pressure in the upper extremities following surgery, the disappearance of signs of severe congestive heart failure, and the appearance of strong femoral artery pulsations. At the time of the child's second hospital admission, mean blood pressures in the upper extremities were again elevated. Signs of congestive failure had reappeared and femoral artery pulsations were no longer palpable. Despite a technically satisfactory repair at the second operation, the weakened and hypoplastic left ventricle failed.

Since the etiology of coarctation of the aorta is not known, any comment on the cause of restenosis of a coarctation can only be conjectural. Development of coarctation of the aorta may be related to the same mechanism as that which results in the normal closure of the ductus arteriosus. Juxtaposition of the stenotic segment and the ductus in the great majority of instances is consistent with this hypothesis. It is possible that the initial surgical attempt to preserve the anomalous subclavian artery resulted in retention of abnormal tissue with an inherent propensity for constriction. It would seem, in view of these experiences, that the extent of the resection in small infants with coarctation is critical. It is imperative that all abnormal aortic tissue involved in the coarctation be removed because

of the possibility of a redevelopment of the obstructive process.

SUMMARY

Surgical repair of coarctation of the aorta may be necessary in infancy when intensive medical management fails. Successful resection of a coarctation of the aorta in a 2-week-old infant was accomplished. Recurrent stenosis at the anastomotic site was found at re-exploration 6 weeks after the initial operation. Possible factors causing this complication and suggestions for its prevention are discussed.

Dr. Donald G. Mulder
University of California Medical Center
Los Angeles 24, California

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TECHNIQUE OF ENDARTERECTOMY*

WILEY F. BARKER, M.D., AND JACK A. CANNON, M.D.

Los Angeles, California

Recent reports on endarterectomy have been concerned with selection of cases and analysis of results. This report will be concerned primarily with details of surgical technique as presently performed. Failure to follow meticulously the details of technique has caused many poor results in the hands of the operator new to this procedure.

PATHOLOGY

In order to be suitable for surgical treatment, the atherosclerotic vessel must truly be segmental. An adequate inflow tract is no less important than an adequate outflow tract.

The procedure of endarterectomy depends upon the ability to develop a cleavage plane between the atheromatous "sequestrum" and relatively normal medial wall. Where a pure atherosclerotic plaque exists, this is easy. The thinness of the remaining wall may be alarming at first, but is little thinner than a normal wall should be. It appears thin only in comparison to the thickened vessels of atherosclerosis. Superimposed inflammation may make the sequestrum and media more adherent. Calcification sometimes is associated with excessively thinned out areas of media.

OPERATIVE PROCEDURES

The patient is placed supine upon the table. If roentgenograms are to be taken a cassette holder may be placed under the hips.

Anesthesia may be of any type and is best left to the discretion of a competent anesthetist. Thorough and predictably constant relaxation is the only prerequisite. Under most circumstances there should be little need for large quantities of blood, but a large needle placed securely in a vein is a very important safeguard. Nasogastric intubation will usually be necessary because of the severity of the ileus that usually follows operations.

* From the Department of Surgery, University of California Medical Center, Los Angeles, California.

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Aortic-Iliac Endarterectomy

Exposure. The abdomen is opened through a long left paramedian or midline incision. After the usual exploration an attempt should be made to evaluate the status of the iliac arteries. Evaluation of the renal, superior mesenteric, and hypogastric arteries is also important.

Exposure of the aorta may be gained without complete displacement of the intestines; the initial incision in the root of the small bowel mesentery may be extended around the tip of the cecum and up the lateral gutter, if complete intestinal mobilization becomes necessary (fig. 1). Exposure of both common iliac arteries is obtained with the primary incision. Exposure of the right external iliac is achieved by extending the original incision down over the vessel, avoiding injury to the ureter. If the right colon is to be mobilized, the spermatic vessels must be handled with care.

If lumbar sympathectomy is to be done, it is best done at this point. The left lumbar chain is readily identified in the groove between the aorta and the bodies of the vertebra. The right chain lies in a comparable position but usually requires additional dissection, whereas exposure of the aorta has exposed the left chain. The chain together with as much of all rami as can be seen is removed from the bottom of the third lumbar disc to the top of the second lumbar body. More extensive upward dissection is unjustified, if adequate reconstruction is possible. Extensive sympathectomy not only interferes with ejaculatory mechanisms but also seems to be associated with a more severe and more protracted postsympathectomy neuralgia.

Isolation of blood vessels. Control of the vessels should be obtained by careful dissection at the level of the terminal aorta and the common iliac, external iliac (below the obstruction), and the hypogastric arteries (fig. 2). Ordinarily, the distal aorta is prepared for cross-clamping below the inferior mesenteric artery. Heavy umbilical tape or fine Penrose tubing may be used to mark and provide emergency control of the vessel. They

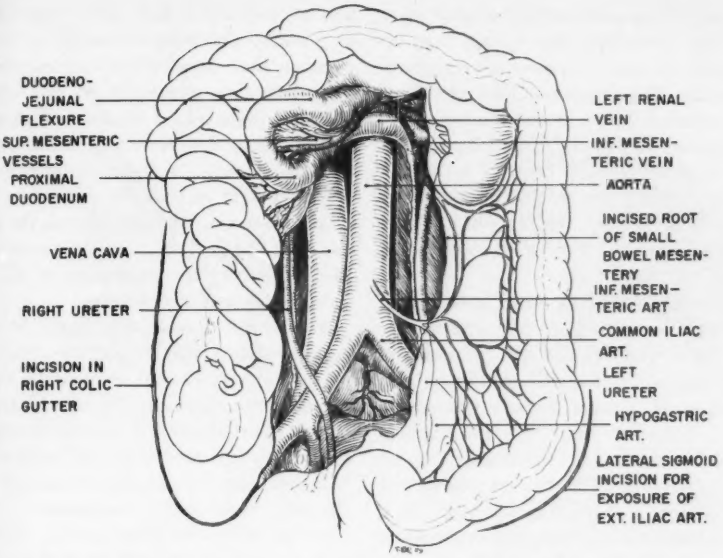

FIG. 1. Anatomical landmarks in exposure of the aorta and iliac arteries

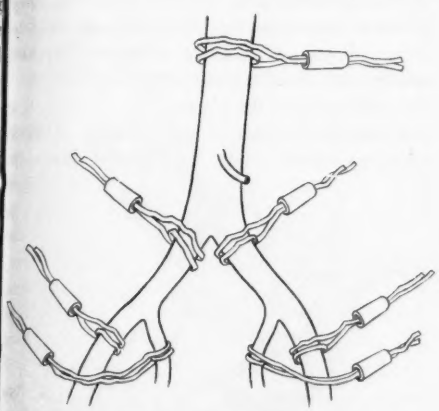

FIG. 2. Common sites for placement of tapes for control of flow before opening the arteries.

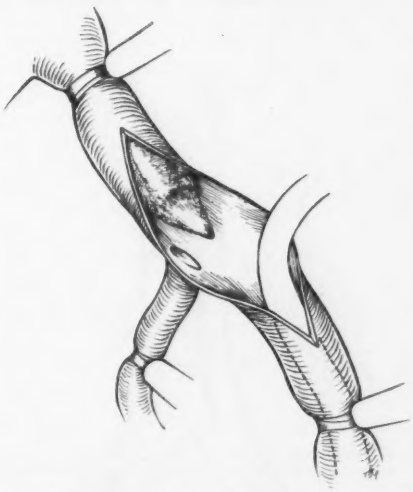

FIG. 3. Placement of catheter in distal arterial tree. Proximal atheroma as yet untouched.

should be placed twice around the vessel in question, not only to provide better control of blood flow, but also to avoid undue injury to the vessel. The middle sacral and major lumbar branches should be controlled with small bulldog clamps, and should not be sacrificed.

When considerable pressure exists in the distal tree, cross-clamping with a noncrushing arterial clamp may be necessary. It is better, if possible, however, to insert a rubber catheter (fig. 3) of a size commensurate with the distal lumen into the vessel, and control backflow around the catheter with the previously placed tapes. Through this catheter one may inject distally heparin or radiopaque contrast media. Back bleeding through the catheter may be controlled by any appropriate clamp applied to the rubber itself.

It is preferable to use longitudinal arteriotomies because of their versatility; that is, they may be easily extended to meet unexpected situations during dissection. Repair is easier and safer than transverse incisions. When performed carefully, no narrowing even in vessels too small for end-to-end suture is produced. The "patch" technique suggested by DeBakey and associates[3] may be of some use in some narrow vessels, but we have not had sufficient experience with it for critical evaluation.

One arteriotomy should be made at the distal limit of thickening on either side and should invariably allow exposure of the hypogastric orifice. The upper arteriotomy should extend from the terminal aorta a short distance into either common iliac artery in order to allow accurate exposure of the carina of the bifurcation (fig. 4).

If equal degrees of obstruction are present, the order of procedure makes little difference. It is useful, wherever possible, to initiate the procedure on one side, carry the dissection up into the aorta and *down* the opposite iliac artery as far as the site of control, to complete the repair of one side and to re-establish flow down that side as soo as possible. The point of control in the opposit common iliac vessel allows one to proceed wit that dissection separately. If one side is onl partially occluded, it should be operated upo first and good flow re-established as promptly a possible, because a less satisfactory collatera will be present on that side.

After assuring complete control, the aorta may be cross-clamped and endarterectomy begun. Mobilization of the full length of the vessels is unnecessary and inadvisable.

The actual dissection is begun at the distal point of obstruction. Usually the atheroma tapers off into a point shaped plaque, and this tip can be mobilized with the tip of a Freer elevator (fig. 5). This allows one to enter the proper sub-intimal plane immediately, and extend it upward with the dissector, making an actual tunnel at the upper limit of the arteriotomy.

On occasion, the distal portion of the plaque seems to extend completely out of the abdomina field as a fibrous posterior ribbon (figs. 6 to 8). I one can be assured of a patent distal tree, one is justified in beveling this edge, suturing the distal intima down and working upwards. The most satisfactory results occur when one can reach the lower limit of the plaque.

Hypogastric artery. If not already in place, catheters should now be inserted down the

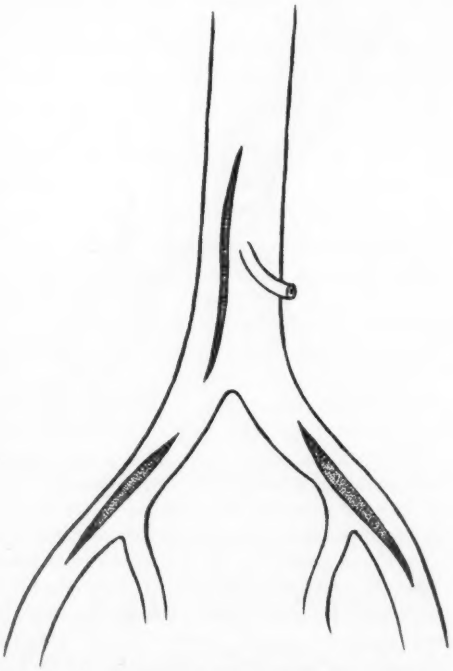

FIG. 4. Site of arteriotomies as usually performed

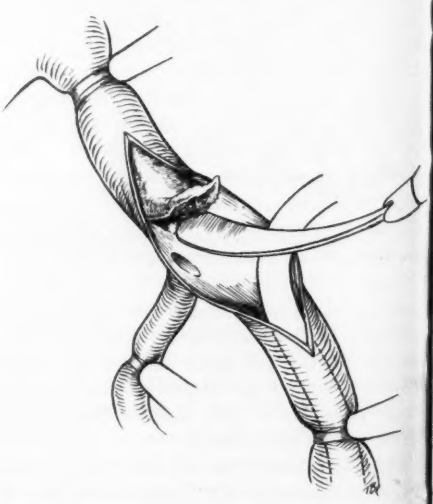

FIG. 5. Mobilization of distal tip of atheromatous plaque.

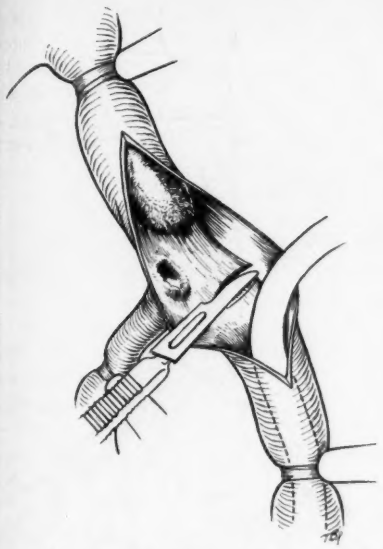

FIG. 6. Beveling of distal edge in extensive posterior intimal thickening.

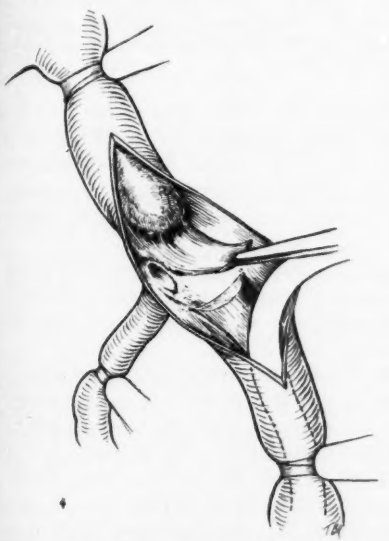

FIG. 7. Dissection of atheromatous strip past patent and minimally involved hypogastric orifice.

femoral segment, and distal heparinization begun. A solution of 10 mg. of heparin per 100 cc. of water is used, and after an initial injection of 10 to 15 cc. of solution, 3 to 5 cc. are introduced every 15 minutes until removal of the catheter.

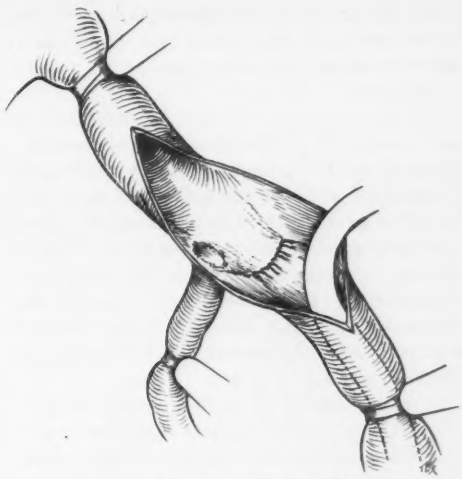

FIG. 8. Suture attachment of hypogastric and distal iliac intima. Figure-of-8 mattress sutures are used, and the knots lie outside the vessel.

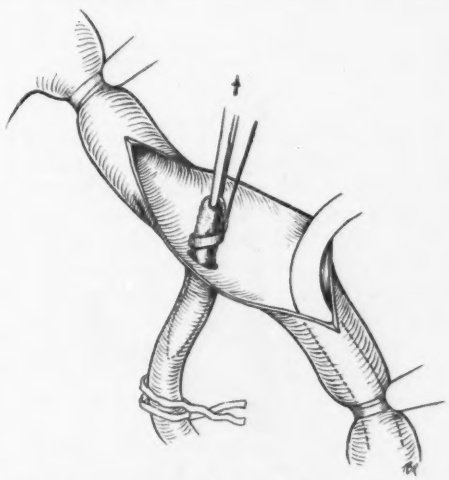

FIG. 9. Dissection of a core of atheroma from an obstructed hypogastric artery.

The arm of the plaque extending into the hypogastric artery should be divided. If the hypogastric orifice is widely patent, it will be sufficient to be sure that there is no subintimal dissection, using fine arterial suture, if necessary, to hold the intima down to the media (fig. 8). When a major plaque extends into the hypogastric artery, it should be dissected with dissector and loop (fig. 9). The distal limit of

dissection cannot be visualized under these circumstances but a satisfactory flow into at least one of the major hypogastric branches can usually be achieved.

The proper level of subintimal dissection is easily achieved in the aorta. If any question arises, it can be identified by passing the tip of the dissector in the already established plane from the distal arteriotomy, or by continuing the distal dissection upward with a loop dissector. Once so started, the aortic plaque below the clamp may be freed easily, taking care to avoid injury to the vulnerable carina (fig. 10). The opposite proximal iliac plaque may be dissected and divided at the level of control.

After the aorta below the clamp has been cleaned, it is usually apparent that there is considerable plaquing above the clamp. This consists not only of true mural atheroma, but often of a thumb sized mass of loose luminal debris, old clot and atheroma. Both of these may be removed easily and quickly by using temporary manual control of the aorta at the level of the renal arteries, releasing the aortic clamp, and dissecting out the debris. Failure to remove this debris undoubtedly accounts for thrombosis of the repaired segment in operations otherwise technically perfect (fig. 12).

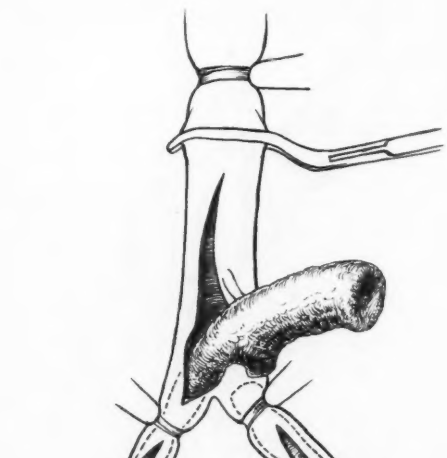

FIG. 10. Removal of the aortic and right iliac sequestrum. Dissection of left iliac artery occlusion could be performed now after closure of the aortic and right iliac arteriotomies and after flow is re-established into the right side.

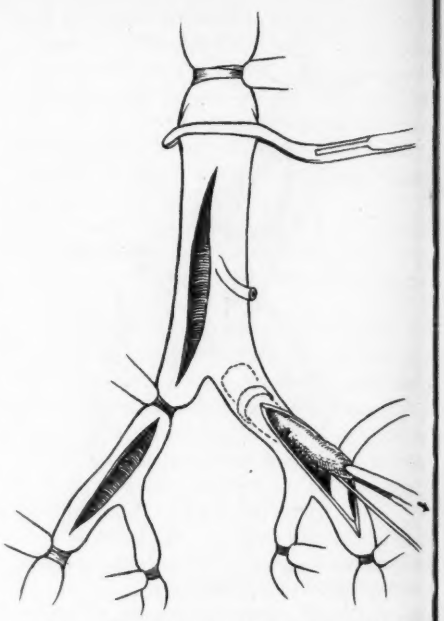

FIG. 11. Dissection of the left iliac plaques. As in figure 10, the other arteriotomies may be closed first if desired.

At this point, the patient should be given 25 to 35 mg. of heparin intravenously and the distal aorta above the clamp washed out with dilute heparin.

Repair. Before repairing the arteriotomy, one must be sure that no loose strips of intima exist in the segment between arteriotomies. The catheter in the distal vessel is replaced so as to lead out through the aortic incision. Repair of the distal arteriotomy is done with a running whip stitch. Repair is done from below upwards utilizing the catheter as a stent as long as possible. The vessel wall should not be handled with forceps. If exposure allows, this segment of arterial suture is most expeditiously placed by using a short, straight needle held by a straight hemostat. Adjustment of the needle in the grasp of the hemostat for the next bite can be done with the needle still in the arterial wall, thus

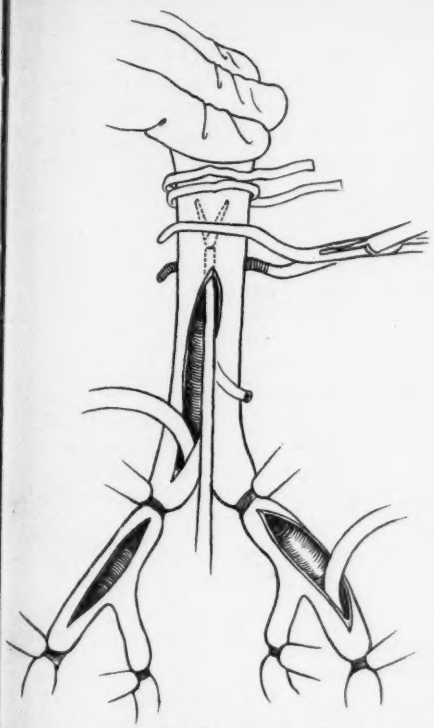

FIG. 12. Removal of debris from the segment of aorta proximal to the clamp before repair.

sparing the wasted motion of pulling the needle through the tissue, lifting needle and needle holder from the wound, adjusting the grasp of the needle holder, and returning to the next bite. With the use of the straight needle one need not take ones eyes or hands from the immediate operative field.

Sutures should be placed no more than 2 mm. wide and 2 mm. apart in these vessels (fig. 13). In smaller vessels, including some small proximal external iliacs, 1 mm. is the maximal bite allowable. If repair is accomplished over the catheter stent there is no fear of narrowing the vessel.

Suture of the aortic incision is most easily begun proximally and is carried as far as possible before removing the catheter. When this point is reached the catheter is withdrawn, irrigating the raw repaired lumen with dilute heparin in passing. Free back flow is assured and any clots at the level of occlusion are washed out. The occluding tapes on the distal tree are again tightened and the aortic clamp momentarily

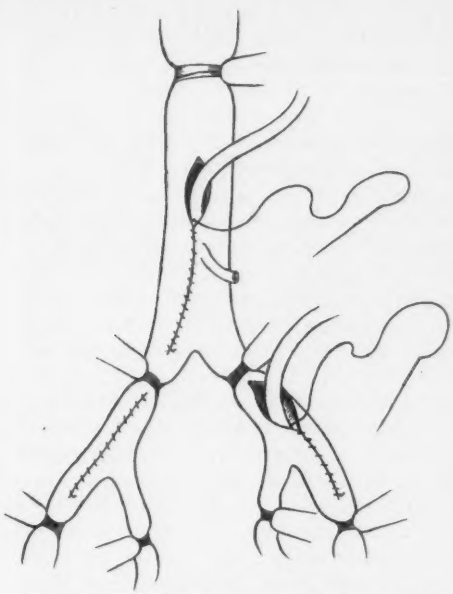

FIG. 13. Final stages of arterial repair, using the intraluminal catheter as a stent as long as possible.

released with proximal manual control. Any clot in the distal aorta should be carefully milked out of the vessel. Closure of the final millimeters of vessel is then completed quickly. Air is flushed from the system by momentary release of the distal tapes before tightening and tying the final suture. All distal tapes are released and if no marked bleeding occurs the aortic clamp may be opened cautiously. It is sometimes necessary to give the patient support with blood at this point as he "bleeds" into a relatively collapsed distal tree.

Marked continuous bleeding from the suture line will sometimes demand further individual sutures for control. Most bleeding from the suture line will be limited to less than 50 cc. and will readily be controlled by simple pressure for 2 or 3 minutes.

Closure. The posterior peritoneal incisions are carefully closed. Drainage is usually not needed. Abdominal closure is routine.

Femoropopliteal endarterectomy has been carefully described elsewhere[2] and will not be detailed here. The same principles apply here as with aortic-iliac endarterectomy. The distal dissection is done first and arteriography is

usually performed to confirm the presence of a good runoff bed. Blind distal stripping has on occasion been successful, but should not be undertaken without considerable experience by the surgeon. It is usually possible to pass the loop stripper proximally the full length of the femoropopliteal segment. If the arteriotomy lies in the lower popliteal vessel, it is usually necessary to unroof the adductor hiatus and make an additional arteriotomy at the level of origin of the superior geniculate arteries. At any time that significant resistance to the stripper is encountered, the artery should be exposed and an arteriotomy made. An incision is easier to repair than a tear.

If absolutely necessary, the artery can be incised through its full length. Repair is tedious but can be facilitated by the use of the straight needle. Such a technique is preferable to inadvertently tearing the vessel at a site where the stripper fails to pass easily, because of intimal plaquing or adherence.

In most instances the upper extent of the endarterectomy should include the orifice of the superficial femoral artery; there is often significant atherosclerosis at this level.

If femoral endarterectomy is to be combined with aortic or iliac dissection, the lower portion should be done first in order to be sure of a good runoff. In the event that the stripping loop is to be passed into the pelvis from the femoral site, one often needs to control the major branches just at the level of the inguinal ligament; that is, the inferior epigastric, superficial circumflex iliac, and the occasional aberrant obturator arteries. Care must also be taken to follow the abrupt medial curve of the vessel into the pelvis.

The femoral catheter stent should be left in place until the pelvic repair is almost completed. It is withdrawn, the femoral arteriotomy closed, the pelvic stents withdrawn, iliac arteriotomies closed, and full flow re-established as quickly as possible.

POSTOPERATIVE CARE

In most instances a short segment needs no heparinization. In longer segmental involvement, heparin is useful to preclude clotting in the presence of the slower stream secondary to the long narrow tube. From an experimental point of view, heparin may be useful in reducing fibrin deposition on the wall to a minimum; the presence of gross clot inhibits the rate of re-endothelialization.[1] For this reason in almost all cases heparinization is maintained for 24 to 48 hours. Where peripheral pulses are slow to appear or are of poor quality, heparin may be useful not only as an anticoagulant but also because of its effect on blood viscosity.[2]

Antibiotics are not used prophylactically.

Ambulation of the patient with aortic and iliac lesions may be as prompt as desired. In femoral endarterectomy, ambulation should be more cautiously approached.

SUMMARY

A brief review is presented of the technical aspects of exposure, choice of arteriotomy sites, repair of the vessel wall and postoperative care in the performance of thromboendarterectomy.

Dr. Wiley F. Barker
University of California Medical Center
Los Angeles 24, California

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